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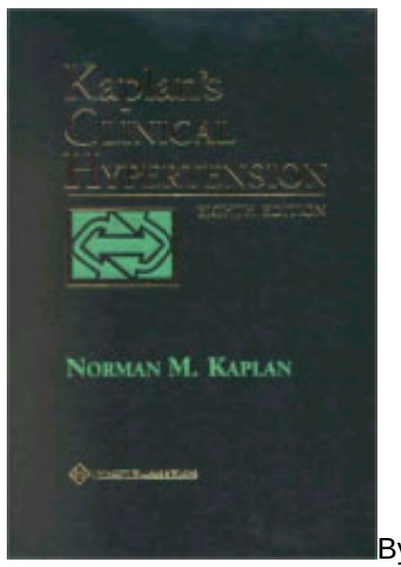

By OkDoKeY

Kaplan’s Clinical Hypertension

Contents

To those such as:

Goldblatt and Grollman,

Braun-Menéndez and Page,

Lever and Pickering,

Mancia, Brenner, and Laragh,

Julius, Hansson, and Freis,

And the many others,

whose work has made it possible for me to put together what I hope will be a useful book on clinical hypertension

NORMAN M. KAPLAN, M.D.
Clinical Professor of Medicine
Department of Internal Medicine
University of Texas Southwestern Medical School
Dallas, Texas

with a chapter by

ELLIN LIEBERMAN, M.D.
Emeritus Professor of Pediatrics
University of Southern California School of Medicine
Los Angeles, California

Editorial Consultant

WILLIAM NEAL, M.D.
John Peter Smith Hospital
Fort Worth, Texas

Preface

TO THE EIGHTH EDITION

This book represents the distillation of a tremendous volume of literature, filtered through the receptive and, I trust, discriminating awareness of a single author. When I wrote the first edition in 1973, the task was challenging, mainly because few had tried a synthesis of what was then known. But—as most who read this book are well aware—in the ensuing 30 years, the task has become much more difficult, mainly because the literature on hypertension has grown so that it is almost beyond the grasp of any one person. I continue to be a single author (with the important exception of the chapter on children) for these two reasons:

- First, a single-authored text offers more cohesion and completeness, and, at the same time, brevity and lack of repetition, compared to most multiauthored but rarely edited megabooks.
- Second, I have the time, energy, and interest to keep up with the literature, and this book has become the major focus of my professional life. The success of the previous editions and the many compliments received from both clinicians in the field and investigators from the research bench have prompted me to do it again.

The very reason that a single-authored text has become such a rarity explains the need for a new edition fairly often. I am amazed at the tremendous amount of hypertension-related literature published over the past 4 years. A considerable amount of significant new information is included in this edition, presented in a manner that I hope enables the reader to grasp its significance and place it in perspective. As with previous editions, almost every page has been revised, using the same goals:

- Give more attention to the common problems; primary (essential) hypertension takes up almost half of the book.
- Cover every form of hypertension at least briefly, providing references for those seeking more information. Additional coverage is provided on some topics that have recently assumed importance, ranging from the impacts of the mapping of the human genome and data from large clinical trials to the roles of cytokines and oxidative stress in the pathogenesis of hypertension.
- Include the latest data, even if available only in abstract form.
- Provide enough pathophysiology to permit sound clinical judgment.
- Be objective and clearly identify biases. Although my views may differ from those of others, I have tried to give reasonable attention to those with whom I disagree.

Once again, I am pleased that Dr. Ellin Lieberman, former head of Pediatric Nephrology at the Children's Hospital of Los Angeles, has contributed a chapter on hypertension in children and adolescents. I have been fortunate in being in an academic setting wherein such endeavors are nurtured, much to the credit of my former chief, Dr. Donald Seldin, and my current chief, Dr. Daniel Foster. I appreciate the help of my editorial consultant, Dr. William Neal, and, in particular, the diligent and timely work of my secretary, Ms. Vicki Martin, as well as the publisher's staff who worked on this edition. And last, the forbearance of Audrey, my wife, can be acknowledged only by the promise that I will not do it again—at least for another 4 years.

This edition, in addition to having the latest information, has been redesigned so that it remains both concise and approachable. I trust that everyone will find it more reader-friendly.

Norman M. Kaplan, M.D.

1
Hypertension in the Population at Large

As the population becomes older and more obese, the number of people with hypertension continues to increase. In developed societies worldwide, most people will develop hypertension during their lifetime. As a consequence of the increased awareness of the damage of hypertension and with the recognition that the progress of hypertension-induced cardiovascular diseases can be slowed by its treatment, the management of hypertension now is the most common indication for visits to physicians by nonpregnant adults in the United States (Cherry et al., 2001). According to the National Ambulatory Medical Care Survey, almost 400 million blood pressure (BP) measurements were taken in 1998 (Woodwell, 2000).

These leading positions are reflected in the data from surveys of a representative sample of the U.S. population, the National Health and Nutrition Examination Surveys (NHANESs), taken over the last 25 years. As seen in Table 1-1, the percentages of people in the United States who are aware of their hypertension, who are being treated, and whose disease is controlled (defined as BP lower than or equal to 140/90 mm Hg) rose considerably from the late 1970s to the mid-1990s [Joint National Committee (JNC), 1997]. Moreover, the prevalence of hypertension appears to have diminished, perhaps because more people have modified lifestyles and thereby lowered their BP (Wolz et al., 2000). However, the lower prevalence figures may reflect improvements in the techniques of measuring BP between NHANES II and III rather than a true decrease (Burt et al., 1995a).

Hypertension	NHANES II, 1976–1980 (%)	NHANES III, phase 1, 1988–1991[a] (%)	NHANES III, phase 2, 1991–1994 (%)
Awareness[a]	51.0	73.0	68.4
Treated[a]	31.0	55.0	53.5
Controlled[a]	10.0	29.0	27.4

NHANES, National Health and Nutrition Examination Survey.
[a]Adults (ages 18 to 74 years) with hypertension (systolic blood pressure of 140 mm Hg or diastolic blood pressure of 90 mm Hg) or taking antihypertensive medication.
[b]Systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg.
Reprinted from Joint National Committee. The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 1997;157:2413–2446, with permission.

TABLE 1-1. *Hypertension awareness, treatment, and control in adults: United States, 1976–1994*

As is described, these improvements in the recognition and treatment of hypertension have played a role in the major reductions in cardiovascular disease seen in the United States over the past decades (Hunink et al., 1997). However, these improvements are not nearly enough: Most hypertension remains uncontrolled, and the most recent NHANES (phase 2) data suggest a slippage both in awareness and control over the last few years (Table 1-1).

In the United States and elsewhere (Cruickshank et al., 2001; EUROASPIRE I and II Group, 2001), hypertension remains a common and serious problem, contributing in a major way to the most common causes of morbidity and mortality in developed societies. Moreover, the main burdens associated with hypertension occur not in the relatively few with severe disease but in the masses of patients with BPs that are only minimally elevated (Stamler et al., 1993).

This book summarizes and analyzes the work of thousands of clinicians and investigators worldwide who have advanced our knowledge about the mechanisms behind hypertension and who have provided increasingly effective therapies for its control. Despite their continued efforts, however, hypertension will almost certainly not ever be totally conquered, because it is one of those diseases that, in the words of a *Lancet* editorialist (Anonymous, 1993):

> . . . afflict us from middle age onwards [that] might simply represent “unfavorable” genes that have accumulated to express themselves in the second half of our lives. This could never be corrected by any evolutionary pressure since such pressures act only on the first half of our lives: once we have reproduced, it does not greatly matter that we grow “sans teeth, sans eyes, sans taste, sans everything.”

In this chapter, the overall problems of hypertension for the population at large are considered. I define the disease, quantify its prevalence and consequences, classify its types, and describe the current status of detection and control. Chapter 2 covers the measurement of BP and the management of its variability.

CONCEPTUAL DEFINITION OF HYPERTENSION

Although it has been more than 100 years since Mahomed clearly differentiated hypertension from Bright's renal disease, authorities still debate the level of BP that is considered abnormal (O'Brien and Staessen, 1999). Sir George Pickering for many years challenged the wisdom of that debate and decried the search for an arbitrary dividing line between normal and high BP. In 1972, he restated his argument: “There is no dividing line. The relationship between arterial pressure and mortality is quantitative; the higher the pressure, the worse the prognosis.” He viewed arterial pressure “as a quantity and the consequence numerically related to the size of that quantity” (Pickering, 1972).

However, as Pickering realized, physicians feel more secure when dealing with precise criteria, even if the criteria are basically arbitrary. To consider a BP of 138/88 mm Hg normal and one of 140/90 high is obviously arbitrary, but medical practice requires that some criteria be used to determine the need for workup and therapy. The criteria should be established on some rational basis that includes the risks of disability and death associated with various levels of BP as well as the ability to reduce those risks by lowering the BP. As stated by Rose (1980), “The operational definition of hypertension is the level at which the benefits. . . . of action exceed those of inaction.”

Even this definition should be broadened, because action (i.e., making the diagnosis of hypertension at any level of BP) involves risks and costs as well as benefits, and inaction may provide benefits. These are summarized in Table 1-2. Therefore, I proposed that the conceptual definition of hypertension be “that level of BP at

which the benefits (minus the risks and costs) of action exceed the risks and costs (minus the benefits) of inaction" (Kaplan, 1983).

Action	Benefits	Risks and costs
Action	Reduce risk of cardiovascular disease, debility, and death Decrease monetary costs of catastrophic events	Assume psychological burdens of the hypertensive patient Interfere with quality of life Require changes in lifestyle Add risks and side effects from therapy Add monetary costs of health care
Inaction	Preserve nonpatient role Maintain current lifestyle and quality of life Avoid risks and side effects of therapy Avoid monetary costs of health care	Increase risk of cardiovascular disease, debility, and death Increase monetary costs of catastrophic events

TABLE 1-2. *Factors involved in the conceptual definition of hypertension*

Most elements of this conceptual definition are fairly obvious, although some, such as interference with lifestyle and risks from biochemical side effects of therapy, may not be. Let us turn first to the major consequence of inaction, the increased incidence of premature cardiovascular disease, because that is the prime, if not the sole, basis for determining the level of BP that is considered abnormal and is called *hypertension*.

Before proceeding, a disclaimer seems appropriate. Many may regard the next few pages as unnecessary academic theory versus the realities of clinical practice. Certainly, many physicians—more in the United States than elsewhere—treat any BP that exceeds 140/90 mm Hg, often before the level has been corroborated, assuming that the known risks and patient's desires demand immediate therapy. As noted further in Chapter 5, we are victims of our very success in promoting hypertension as "the silent killer." Nonetheless, caution is advisable. Mae West once said, "too much of a good thing is wonderful," but she was *not* referring to the treatment of hypertension. Consideration of the benefits as well as the risks and costs of therapy is appropriate, so that patients may receive more of the benefits and fewer of the risks and costs.

Risks of Inaction: Increased Risk of Cardiovascular Disease

The risks of elevated BP have been determined from large-scale epidemiologic surveys. MacMahon et al. (1990) performed a metaanalysis of all available major prospective observational studies relating diastolic BP level to the incidence of stroke and coronary heart disease (CHD). In the nine studies analyzed, almost 420,000 people were followed up for 6 to 25 years. A total of 599 fatal strokes and 4,260 deaths from CHD were recorded.

As seen in Figure 1-1, the overall results demonstrate "direct, continuous and apparently independent associations" with "no evidence of any 'threshold' level of diastolic BP below which lower levels of diastolic BP were not associated with lower risks of stroke and CHD." In reaching this conclusion, MacMahon et al. (1990) considered the common practice in all nine studies of measuring BP only once, which leads to a substantial underestimation of the true association between the usual or long-term average BP and disease. By applying a correction factor based on three sets of readings recorded over 4 years in the Framingham study to all nine sets of data, MacMahon et al. (1990) came up with estimates of risk that are approximately 60% greater than those previously published using uncorrected data. They estimate that a diastolic BP that is persistently higher by 5.0 mm Hg is associated with at least a 34% increase in stroke risk and at least a 21% increase in CHD risk.

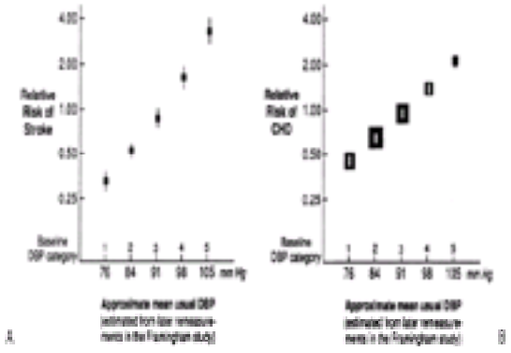

FIG. 1-1. Relative risk of stroke **(A)** and coronary heart disease (CHD) **(B)**, estimated from the combined results of prospective observational studies for five categories of diastolic blood pressure (DBP). (Estimates of the usual DBP in each baseline DBP category are from mean DBP values in the Framingham study recorded 4 years after baseline measurement.) The stroke data were obtained from seven prospective observational studies (n = 843 events). The CHD data were obtained from nine prospective observational studies (n = 4,856 events). The solid squares represent disease risk in each category relative to risk in the entire study population (square size is proportional to the number of events in each DBP category). Vertical lines represent 95% confidence intervals for the estimates of relative risk. (From MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765–773, with permission.)

Gender and Risk

A total of 96% of subjects followed up in the nine epidemiologic surveys analyzed by MacMahon et al. (1990) were men. Studies of women have shown that they tolerate hypertension better than do men and have lower coronary mortality rates with any level of hypertension (Barrett-Connor, 1997; Isles, 1995). Although it takes higher BPs to hurt women, when their pressures are high, they do suffer the consequences, as shown in the Framingham study (Fig. 1-2) (Kannel, 1996).

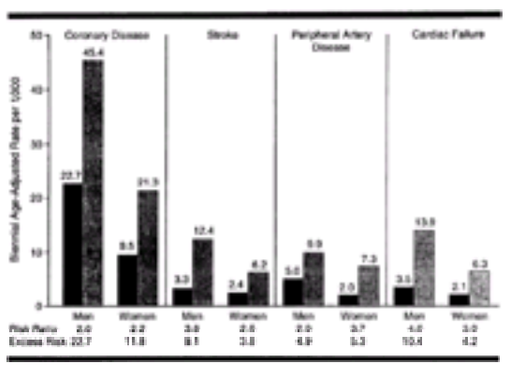

FIG. 1-2. Risks of cardiovascular events by hypertensive status in men and women aged 35 to 64 years, from the Framingham study at 36-year follow-up. Coronary disease includes clinical manifestations of disease, such as myocardial infarction, angina pectoris, sudden death, other coronary deaths, and coronary insufficiency syndrome; peripheral artery disease is manifested as intermittent claudication. The biennial age-adjusted rate is per 1,000 people at risk. Shaded bars, subjects with hypertension; solid bars, normal subjects. (From Kannel WB. Blood pressure as a cardiovascular risk factor. JAMA 1996;275:1571–1576, with permission.)

Race and Risk

Blacks tend to have higher levels of BP than do nonblacks, and overall hypertension-related mortality rates are higher among blacks (Gillum, 1996). In the Multiple Risk Factor Intervention Trial, which involved more than 23,000 black men and 325,000 white men who were followed up for 10 years, an interesting racial difference was confirmed: The mortality rate of CHD was lower in black men with a diastolic BP exceeding 90 mm Hg than in white men (relative risk, 0.84), but the mortality rate of cerebrovascular disease was higher (relative risk, 2.0) (Neaton et al., 1989).

The greater risk of hypertension among blacks suggests that more attention must be given to even low levels of hypertension among this group, but there seems little reason to use different criteria to diagnose hypertension in blacks than in whites. The special features of hypertension in blacks are discussed in more detail in Chapter 4.

The relative risk of hypertension differs among other racial groups as well. In particular, hypertension rates in U.S. Hispanics are similar to or lower than those for whites; and despite their higher prevalence of obesity and diabetes, Hispanics have lower rates of cardiovascular disease than do whites (Ramirez, 1996).

Age and Risk: The Elderly

The number of people older than 65 years is rapidly increasing and, in fewer than 30 years, one of every five people in the United States will be older than 65 (Spillman and Lubitz, 2000). As seen in Figure 1-3, systolic BP rises progressively with age (Burt et al., 1995b), and elderly people with hypertension are at greater risk for cardiovascular disease.

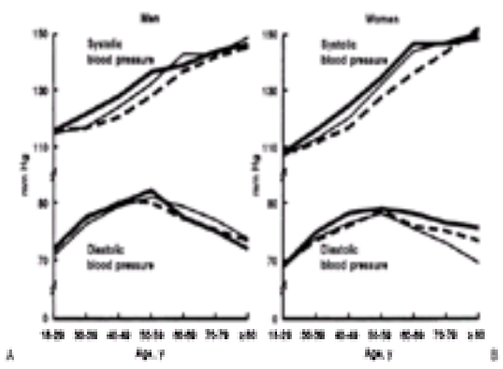

FIG. 1-3. Mean systolic and diastolic blood pressures by age and race or ethnicity for men **(A)** and women **(B)** in the U.S. population 18 years of age or older. Thick solid line, non-Hispanic blacks; dashed line, non-Hispanic whites; thin solid line, Mexican-Americans. Data from the NHANES III survey. (From Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995b;25:305–313, with permission.)

Pulse Pressure

During the last few years, a virtual explosion of evidence has confirmed the greater prognostic influence of pulse pressure—the difference between the systolic and diastolic BP—over either systolic or diastolic levels, particularly in the elderly (Darne et al., 1989; Franklin et al., 1999; Khattar et al., 2001). As seen in Figure 1-3, systolic levels rise progressively with age, whereas diastolic levels typically start to fall beyond age 50. Both of these changes reflect increased aortic stiffness and pulse-wave velocity with a more rapid return of the reflected pressure waves (Asmar et al., 2001), as are described in more detail in Chapter 3. It therefore comes as no surprise that the progressive widening of pulse pressure is the best prognosticator of cardiovascular risk, as both the widened pulse pressure and most of the risk come from the same pathology—atherosclerosis and arteriosclerosis.

Awareness of the critical nature of the widened pulse pressure began in the late 1980s (Darne et al., 1989) but, as Swales (2000) pointed out, the risk of rising systolic BP actually was recognized in the early 1900s. For somewhat obscure reasons, most of the risks of hypertension were ascribed soon thereafter to the high diastolic levels typically seen in the younger population. From the 1920s until the mid-1980s, the diastolic levels “ruled” (Ramsay and Waller, 1986), even though the Framingham data were shown in 1971 to document the greater predictive value of systolic levels for cardiovascular disease (Kannel et al., 1971). The pervasive influence of diastolic BP is shown in Figure 1-1. In this landmark analysis, only diastolic BPs were used to demonstrate the relationship of hypertension to stroke and coronary disease (MacMahon et al., 1990).

There remains an important role for elevated diastolic levels, particularly in middle-aged women (Benetos et al., 2001). In the Framing-ham Heart Study participants, a gradual shift from diastolic BP to systolic BP and pulse pressure as predictors of coronary risk was noted with increasing age of the participants (Franklin et al., 2001b). At less than age 50, diastolic BP was the strongest predictor of CHD risk. From age 50 to 59, all three indices were comparable predictors. From age 60 on, diastolic BP was negatively associated with risk so that the pulse pressure then became superior to systolic BP.

Moreover, in middle-aged patients with combined systolic and diastolic hypertension, pulse pressure is a stronger predictor of CHD, whereas the BP per se is more closely related to stroke (Verdecchia et al., 2001).

The fall in diastolic BP that typically occurs after age 50 adds to the risk seen with the rising systolic level. These associations were clearly defined in the Framingham population (Franklin et al., 1999). Rising systolic BP adds to CHD risk in concert with a falling diastolic BP (Fig. 1-4A) and a rising pulse pressure (Fig. 1-4B). As with systolic BP, the risk of cardiovascular events increases progressively with increasing pulse pressure.

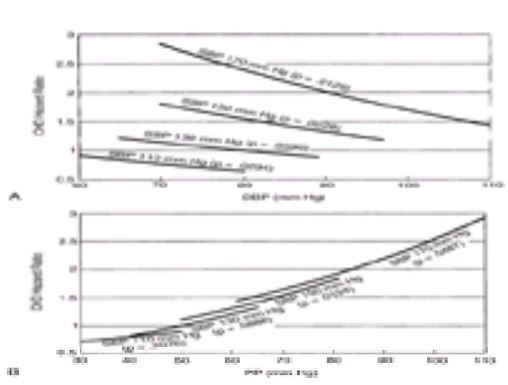

FIG. 1-4. Joint influences on coronary heart disease (CHD) hazard ratio of systolic blood pressure (SBP) with **(A)** diastolic blood pressure (DBP) and with **(B)** pulse pressure (PP). The CHD hazard ratios were set to a reference value of 1.0 for an SBP of 130 mm Hg and a DBP of 80 mm Hg **(A)** or pulse pressure of 50 mm Hg **(B)**. (Modified from Franklin SS, Khan SA, Wong ND, et al. Is pulse pressure useful in predicting risk for coronary heart disease? Circulation 1999;100: 354–360.)

Isolated Systolic Hypertension

As expected from Figure 1-3, most hypertension after age 50 is isolated systolic hypertension (ISH), with a diastolic BP of less than 90 mm Hg. In an analysis based on the NHANES III data, Franklin et al. (2001a) found that ISH was the diagnosis in 65% of all cases of uncontrolled hypertension seen in the entire population and in 80% of patients older than 50. It should be noted that, unlike some reports that define ISH as a systolic BP of 160 or higher, Franklin et al. (2001a) appropriately use 140 or higher.

ISH is associated with increased morbidity and mortality from coronary disease and stroke in patients as old as 94 years (Kannel et al., 1997). However, as older patients develop cardiovascular disease and cardiac pump function deteriorates, systolic levels often fall and a U-shaped curve of cardiovascular mortality becomes obvious: Mortality increases both in those with systolic BP of less than 120 and in those with systolic BP of more than 140. Similarly, mortality is higher in those 85 years or older if their systolic BP is lower than 125 or their diastolic BP is lower than 65, both indicative of poor overall health (Boshuizen et al., 1998).

Relative versus Absolute Risk

In most of the data presented to this point, the risks of elevated BP have been presented as relative to risks found with lower levels of BP. This way of looking at risk tends to exaggerate its degree, as is described in Chapter 5, in which the benefits of therapy and the decision to treat are discussed. For now, a single example should suffice. As seen in Figure 1-5, when the associations among various levels of BP and the risk of having a stroke were examined in 450,000 patients who were followed up for 5 to 30 years, a clear increase in stroke risk was seen with increasing levels of diastolic BP (Prospective Studies Collaboration, 1995). In relative terms, the increase in risk was much greater in the younger group (<45 years), rising from 0.2 to 1.9, which is nearly a tenfold increase in relative risk as compared to the less than twofold increase in the older group (10.0 to 18.4). However, it is obvious that the *absolute* risk is much greater in the elderly, with 8.4% (18.4 minus 10.0) more having a stroke with the higher diastolic BP as compared to only 1.7% (1.9 minus 0.2) more of the younger patients. The importance of this increased risk in the young with higher BP should not be ignored, but the use of the smaller change in absolute risk rather than the larger change in relative risk seems more appropriate when applying epidemiologic statistics to individual patients.

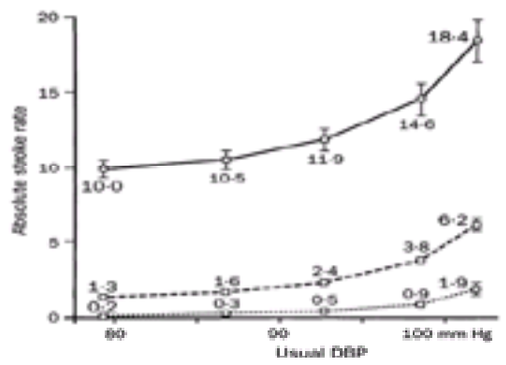

FIG. 1-5. The absolute risks for stroke by age and usual diastolic blood pressure (DBP) in 45 prospective observational studies involving 450,000 individuals with 5 to 30 years of follow-up during which 13,397 participants had a stroke. Dotted line, <45 years old; dashed line, 45–65 years old; solid line, >65 years old. (Data from Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Lancet 1995;346:1647–1653.)

The distinction between the risks for the population and for the individual is important. For the population at large, risk clearly increases with every increment in BP, and levels of BP that are accompanied by significantly increased risks should be called *high*. As Stamler et al. (1993) note, “Among persons aged 35 years or more, most have BP above optimal (<120/<80 mm Hg); hence, they are at increased CVD [cardiovascular disease] risk, i.e., the BP problem involves most of the population, not only the substantial minority with clinical hypertension.” However, for individual patients, the absolute risk from slightly elevated BP may be very small. Therefore, more than just the level of BP should be used to determine risk and, even more important, to determine the need to institute therapy (Pocock et al., 2001). This is covered in detail in Chapter 5.

Benefits of Action: Decreased Risk of Cardiovascular Disease

Let us now turn to the major benefit (listed in Table 1-2) that is involved in a conceptual definition of hypertension, the level at which it is possible to show the benefit of reducing cardiovascular disease by lowering the BP. Inclusion of this factor is predicated on the assumption that it is of no benefit—and, as we shall see, is potentially harmful—to label a person hypertensive if nothing will be done to lower the BP.

Natural versus Treatment-Induced Blood Pressure

Before proceeding, one caveat is in order. As noted earlier, less cardiovascular disease is seen in people with low BP who are not receiving antihypertensive therapy. However, that fact cannot be used as evidence to support the benefits of therapy, because naturally low BP may offer a degree of protection not provided by a similarly low BP resulting from antihypertensive therapy.

The available evidence supports that view: Morbidity and mortality rates, particularly those of coronary disease, continue to be higher in many patients at relatively low risk who are undergoing antihypertensive drug treatment than in untreated people with similar levels of BP. This has been shown in follow-up studies of multiple populations (Andersson et al., 1998; Clausen and Jensen, 1992; Thürmer et al., 1994). This issue, too, is covered in more detail in Chapter 5, but one piece of the evidence is acknowledged here.

An analysis of all-cause and cardiovascular mortality observed in seven randomized trials of middle-aged patients with diastolic BP ranging from 90 to 114 mm Hg showed a reduction in mortality in the treated patients in those trials wherein the population was at fairly high risk, as defined by an all-cause mortality rate of greater than 6 per 1,000 person-years in the untreated population (Hoes et al., 1995). However, in those studies involving patients who started at a lower degree of risk, those who were treated had *higher* mortality rates than were seen in the untreated groups.

These disquieting data should not be taken as evidence against the use of antihypertensive drug therapy. They do not, in any way, deny that protection against cardiovascular complications can be achieved by successful reduction of BP with drugs in patients at risk. They simply indicate that the protection may not be universal or uniform for one or more reasons, including the following: (a) only a partial reduction of BP may be achieved; (b) irreversible hypertensive damage may be present; (c) other risk factors that accompany hypertension may not be improved; and (d) dangers are inherent to the use of some drugs, in particular the high doses of diuretics used in the earlier trials covered by Hoes et al. (1995). Whatever the explanation, these data document a difference between natural and induced levels of BP.

Rationale for Reducing Elevated Blood Pressure

In contrast to the data just cited, considerable experimental, epidemiologic, and clinical evidence indicates that reducing elevated BP is beneficial, particularly in high-risk patients (Blood Pressure Lowering Treatment Trialists' Collaboration, 2000). Table 1-3 presents the rationale for lowering elevated BP. The reduction in cardiovascular disease and death (listed last in the table) can be measured to determine the BP level at which a benefit is derived from antihypertensive therapy. That level can be used as part of the operational definition of hypertension.

Morbidity and mortality as a result of cardiovascular diseases are directly related to the level of blood pressure.
Blood pressure rises most in those whose pressures are already high.
In humans, there is less vascular damage where the blood pressure is lower: beneath a coarctation, beyond a renovascular stenosis, and in the pulmonary circulation.
In animal experiments, lowering the blood pressure has been shown to protect the vascular system.
Antihypertensive therapy reduces cardiovascular disease and death.

TABLE 1-3. *Rationale for the reduction of elevated blood pressure*

During the last 35 years, controlled therapeutic trials have included patients with diastolic BP levels as low as 90 mm Hg. Detailed analyses of these trials are presented in Chapter 5. For now, it is enough to say that there is no question that protection against cardiovascular disease has been documented for reduction of diastolic BP levels that start at or above 95 mm Hg, but there is continued disagreement about whether protection has been shown for those whose diastolic BP starts at or above 90 mm Hg who are other-wise at low risk. Similarly, protection for the elderly with ISH has been documented with systolic BP of ³160, but no data are available for the large population having a systolic BP between 140 and 160 mm Hg. Therefore, expert committees have disagreed about the minimum level of BP at which drug treatment should begin.

These disagreements have highlighted the need to consider more than the level of BP in making a therapeutic decision. As is noted in Chapter 5, the consideration of other risk factors, target organ damage, and symptomatic cardiovascular disease permits one to make a more rational decision about whom to treat.

Prevention of Progression of Hypertension

Another benefit of action is the prevention of progression of hypertension, which should be looked on as a surrogate for reducing the risk of cardiovascular disease. Evidence of that benefit is strong, based on data from multiple, randomized, placebo-controlled clinical trials. In such trials, the number of patients whose hypertension progressed from their initially less severe degree to more severe hypertension (defined as BP >200/ 110 mm Hg) was only 95 of 13,389 patients on active treatment versus 1,493 of 13,342 patients on placebo (Moser and Hebert, 1996).

Risks and Costs of Action

The decision to label a person as hypertensive and to begin treatment involves assumption of the role of a patient, changes in lifestyle, possible interference with the individual's quality of life, risks from biochemical side effects of therapy, and financial costs. As is emphasized in the next chapter, the diagnosis should not be based on one or only a few BP readings. In a survey of 6,258 adults in two Canadian cities, Birkett et al. (1987) found that 11.4% had hypertension but that an additional 14.3% had been previously mislabeled as hypertensive. The fact that most U.S. adults have their BP measured every year is thus a mixed blessing: Many who need antihypertensive therapy are identified, but others are misdiagnosed and unnecessarily treated.

Assumption of the Role of a Patient

Merely labeling a person hypertensive may cause negative effects as well as enough sympathetic nervous system activity to change hemodynamic measurements (Rostrup et al., 1991). Although some investigators have found no adverse psychological effects related to a person's awareness of having hypertension (Moum et al., 1990), most do find such effects (Alderman and Lamport, 1990; Robbins et al., 1990). People who know that they are hypertensive may have considerable anxiety over the diagnosis of “the silent killer” and experience multiple symptoms as a consequence (Kaplan, 1997). However, hypertensive people who receive appropriate counseling and comply with therapy usually have no impairment and may have improvements in overall quality-of-life measures (Grimm et al., 1997).

Nonetheless, the consequences of labeling a person as hypertensive may be insidious. For example, the yearly income of 230 hypertensive Canadian steelworkers 5 years after they were identified averaged $1,093 less than that of a matched group of normotensive workers, even though both groups had similar incomes in the year before screening (Johnston et al., 1984).

Changes in Lifestyle and Interferences with Quality of Life

One-third of 3,844 patients who were started on antihypertensive medications for the Hypertension Detection and Follow-up Program experienced side effects; drug treatment was discontinued in approximately one-third of those patients (Curb et al., 1988). In ordinary practice, neither physicians nor patients may be aware of side effects that can impair a patient's quality of life. Jachuck et al. (1982) surveyed 75 consecutive patients from an English group practice who were taking the usual antihypertensive drugs. The patients, their physicians, and their closest relatives were asked a series of questions about the patient's quality of life. Most patients stated that their quality of life had improved or was no different after therapy, and all the physicians stated that the patients had improved. However, 99% of the relatives said that the patients' quality of life was worse after therapy, describing memory loss (33%), irritability (45%), depression (46%), hypochondria (55%), and decreased sexual interest (64%).

This study, although small in scope and uncontrolled, suggests that treatment of hypertension, at least as it was provided in the 1980s, may interfere with a patient's enjoyment of life in ways of which neither the patient nor the physician may be aware. When objective assessments are used, most patients do not experience any impairment in quality of life (see Chapter 7). Nonetheless, even nondrug therapies, such as a moderate reduction in calories and sodium intake, may be perceived as unpleasant.

Risks from Biochemical Side Effects of Therapy

Biochemical risks are less likely to be perceived by the patient than the interferences with lifestyle, but they may actually be more hazardous. These risks are discussed in detail in Chapter 7. For now, only two will be mentioned: Hypokalemia, which develops in 5% to 20% of diuretic-treated patients, and elevations in serum cholesterol or triglyceride level, which may accompany the use of diuretics or b-blockers.

Overview of Risks and Benefits

Obviously, many issues are involved in determining the level of BP that poses enough risk to mandate the diagnosis of hypertension and to call for therapy, despite the potential risks that appropriate therapy entails. An analysis of issues relating to risk factor intervention by Brett (1984) clearly defines the problem:

> Risk factor intervention is usually undertaken in the hope of long-term gain in survival or quality of life. Unfortunately, there are sometimes tradeoffs (such as inconvenience, expense, or side effects) and something immediate must be sacrificed. This tension between benefits and liabilities is not necessarily resolved by appealing to statements of medical fact, and it is high-lighted by the fact that many persons at risk are asymptomatic. Particularly when proposing drug therapy, the physician cannot make an asymptomatic person feel any better, but might make him feel worse, as most drugs have some incidence of adverse effects. But how should side effects be quantitated on a balance sheet of net drug benefit? If a successful antihypertensive drug causes impotence in a patient, how many months or years of potentially increased survival make the side effect acceptable? There is obviously no dogmatic answer; accordingly, global statements such as “all patients with asymptomatic mild hypertension should be treated” are inappropriate, even if treatment were clearly shown to lower morbidity or mortality rates.

The example of mild hypertension may be developed further. It is widely acknowledged that with successively higher BP levels, the risk of complications increases gradually rather than abruptly. Therefore, the reasons to intervene should be viewed as gradually more compelling as BP rises rather than as suddenly compelling at a specific level such as 90 mm Hg. Guttmacher et al. (1981) argue persuasively that selection of a cutoff for critically elevated BP reflects a value judgment about the point at which a risk is thought to be serious enough to warrant treatment. Each decision must be individualized, depending on the patient's aversion to risk, perception of the intrusiveness of medical care in his or her life, tolerance for discomfort or unto-ward drug effects, and other factors. When the medical database

contains considerable uncertainty, as it does for mild hypertension, the risk-to-benefit calculation is even more difficult.

On the other hand, Julius (2000) has argued that, with currently available antihypertensive drugs, which have few, if any, side effects, therapy should be provided even at BP levels lower than 140/90 mm Hg, to prevent both the progression of BP and target organ damages that occur at “high-normal” levels.

OPERATIONAL DEFINITIONS OF HYPERTENSION

Now that the issues of risk and benefit have been examined, operational definitions of hypertension can be offered. Most of what follows relates to the levels of BP. However, many other factors are involved in the effects of BP on cardiovascular health and disease. Jay Cohn (1998) has suggested that the definition of hypertension be broadened to “a state of abnormal arterial function and structure associated with endothelial dysfunction, vascular smooth muscle constriction or remodeling, increased impedance to left ventricular ejection and propensity for atherosclerosis, often but not always manifested by an elevated blood pressure.” Cohn is correct but, for clinical practice, the numbers are what count.

Sixth Joint National Committee Criteria

Table 1-4 provides the classification of BP from the 1997 report of the sixth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). It includes both systolic and diastolic levels in its classification. The levels shown should be based on at least three sets of readings over several weeks. Hypertension then is categorized by either systolic or diastolic gradation into one of three stages. If the systolic BP and diastolic BP correspond to different stages, the highest stage is used. These three stages should be used instead of the terms *mild*, *moderate*, and *severe*, particularly because most premature cardiovascular events occur in those with so-called mild hypertension.

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal[a]	<120	and	<80
Normal	<130	and	<85
High normal	130–139	or	85–89
Hypertension[c]			
Stage 1	140–159	or	90–99
Stage 2	160–179	or	100–109
Stage 3	>180	or	>110

[a]These definitions apply to adults who are not taking antihypertensive drugs and who are not acutely ill. When systolic and diastolic blood pressure fall into different categories, the higher category should be selected to classify the individual's blood pressure status. Isolated systolic hypertension is defined as systolic blood pressure of 140 mm Hg and diastolic blood pressure of <90 mm Hg and appropriate staging.

[b]Optimal blood pressure with respect to cardiovascular risk is <120 mm Hg systolic and <80 mm Hg diastolic.

[c]Based on the average of two or more readings taken at each of two or more visits after an initial screening.

Data from the Joint National Committee. The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997;157:2413–2446.

TABLE 1-4. *Classification of blood pressure for age adults aged 18 years and older*[a]

Most patients will be correctly staged on the basis of the systolic BP. In 3,656 subjects in the Framingham cohort, 64.6% had congruent stages of systolic BP and diastolic BP, 31.6% were upstaged on the basis of systolic BP, and 3.8% were upstaged on the basis of diastolic BP (Lloyd-Jones et al., 1999a). Thus, systolic BP alone correctly classified nearly 96% of the subjects.

Systolic Hypertension in the Elderly

In view of the recognized risks of isolated systolic elevations (Fig. 1-4), JNC VI recommends that, in the presence of a diastolic BP of less than 90 mm Hg, a systolic BP level of 140 mm Hg or higher be classified as ISH. Although risks of such elevations of systolic BP in the elderly have been clearly identified (Franklin et al., 2001b), the value of therapy to reduce systolic levels between 140 and 160 mm Hg in the elderly has not been tested.

Hypertension in Children

For children, JNC VI uses the definition from the *Report of the Second Task Force on Blood Pressure Control in Children* , which identifies *significant hypertension* as BP persistently equal to or greater than the ninety-fifth percentile for age and height and *severe hypertension* as BP persistently equal to or greater than the ninety-ninth percentile for age and height. Hypertension in children is covered in Chapter 16.

Labile Hypertension

As ambulatory readings have been recorded, the marked variability in virtually everyone's BP has become obvious (see Chapter 2). In view of the usual variability of BP, the term *labile* is neither useful nor meaningful.

Borderline Hypertension

The term *borderline* may be used to describe hypertension in which the BP only occasionally rises above 140/90 mm Hg. Persistently elevated BP is more likely to develop in such people than in those with consistently normal readings. However, this progression is by no means certain. In one study of a particularly fit, low-risk group of air cadets with borderline pressures, only 12% developed sustained hypertension over the subsequent 20 years (Madsen and Buch, 1971). Nonetheless, people with borderline pressures tend to have hemodynamic changes indicative of early hypertension and greater degrees of other cardiovascular risk factors, including greater body weight, dyslipidemia, and higher plasma insulin levels (Julius et al., 1990) and should, therefore, be followed more closely and advised to modify their lifestyle.

Operational Definition Based on Risk and Benefit

Considering all the factors shown in Table 1-2, I believe that hypertension in adults, *based on an average of multiple readings*, should be defined as it is in Table 1-4 (from JNC VI).

In using these levels to make the diagnosis, one major caveat should be recognized: The diagnosis of hypertension does not automatically mean that drug treatment should be given immediately to people with elevated BP levels (see Chapter 5). Moreover, in people highly susceptible to premature cardiovascular disease because of concomitant risk factors or target organ damage, antihypertensive therapy may be needed even for BP levels well below 140/90 mm Hg.

In addition, patients whose BP is not high enough to mandate drug therapy may benefit from being diagnosed as hypertensive if, thereby, they are more willing to modify unhealthy life-style habits. As described in Chapter 6, such life-style modifications may reverse the trend toward progressively higher BP and reduce the level of other cardiovascular risk factors (Sacks et al., 2001).

PREVALENCE OF HYPERTENSION

The best sources of data for the U.S. population are the previously noted NHANES studies, which examine a large representative sample of the U.S. adult population approximately every 10 years.

Prevalence in the Population at Large

The number of adults in the United States with hypertension—defined in the NHANES as those having a systolic BP of 140 mm Hg or higher, a diastolic BP of 90 mm

Hg or higher, or taking antihypertensive drug therapy or having been told by a physician two or more times that they were hypertensive—decreased from nearly 58 million during 1976 to 1980 to approximately 50 million during 1988 to 1994 (Wolz et al., 2000). One possible explanation for this decrease in the prevalence of hypertension involves the setting in which the BP measurements were made in these surveys. In NHANES II (1976–1980), BPs were measured at one visit to special clinics, whereas in NHANES III (1986–1994), three readings were taken at the subjects' homes and three at the clinic several weeks later, and the mean of the six readings was used. In addition, the lower total number may reflect the wider use of lifestyle modifications to lower BP.

These data are averages of only six BP readings taken on two occasions. A person's BP often remains higher than usual on the first and second examination, so the prevalence of persistent hypertension probably is lower than indicated by these data. Nonetheless, as shown in Figure 1-6, the data provide an impressive portrayal of how the prevalence of hypertension continues to rise as the population grows older. Approximately 20% of the entire U.S. population has hypertension at any point in time, and most people will develop it as they grow older.

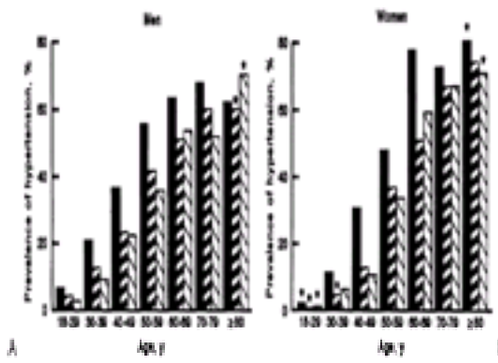

FIG. 1-6. Prevalence of high blood pressure by age and race or ethnicity for men **(A)** and women **(B)** in the U.S. population 18 years of age or older. Solid bars, non-Hispanic blacks; heavy crosshatching, non-Hispanic whites; light cross-hatching, Mexican-Americans; asterisk, estimate based on a sample size that did not meet the minimum requirements of the National Health and Nutrition Examination Survey III (NHANES III) design or relative standard error of the mean >30%. Data from NHANES III. (From Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995b;25:305–313, with permission.)

In the 4,962 subjects in the Framingham cohort examined between 1990 and 1995, the percentages with varying levels of BP were 43.7% optimal or normal, 13.4% high-normal, 12.9% stage 1, and 3.6% stage 2 or greater, and 26.4% were receiving antihypertensive medication (Lloyd-Jones et al., 1999b).

Perhaps a more accurate reflection of the general U.S. population, as it included all ethnic groups and few were on treatment, are the data from the Hypertension Detection and Follow-up Program (Hypertension Detection and Follow-up Program Cooperative Group, 1977). In this study, almost 159,000 people aged 30 to 69 years from 14 communities throughout the United States were examined initially in their homes (Fig. 1-7). Of all participants with a diastolic BP exceeding 90 mm Hg, 67% had stage 1 hypertension (diastolic BP, 90–99 mm Hg), 22% had stage 2 (diastolic BP, 100–109 mm Hg), and 11% had stage 3 (diastolic BP, ³110 mm Hg). The actual prevalence figures are likely too high because they are based on the second measurements taken on the initial home visit. When the participants were reexamined, their BP was usually lower; 44% of the white men with a diastolic BP of 95 to 104 mm Hg on the first screening had a BP of less than 90 mm Hg on the second screening. Nonetheless, the relative distribution of various levels should be correct.

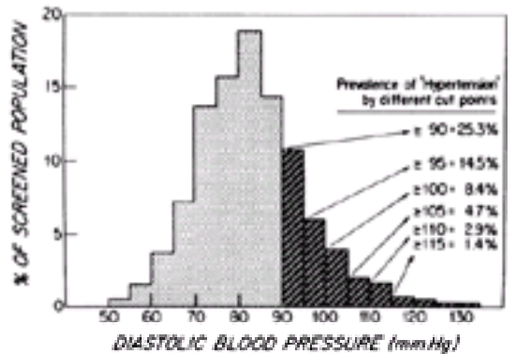

FIG. 1-7. Frequency distribution of diastolic blood pressure measured at home screening (n = 158,906, ages 30 to 69 years). [From Hypertension Detection and Follow-up Program Cooperative Group. The Hypertension Detection and Follow-up Program. A progress report. Circ Res 1977;40(Suppl 1):I106–I109, with permission.]

Prevalence within Racial Groups

The preceding section refers to the overall adult population of the United States. However, the prevalence of hypertension varies among different racial groups within the population. More-over, the prevalence of the disease in other populations may differ from that in the U.S. population.

Blacks

Data from NHANES III show more blacks than whites in the United States have hypertension (Fig. 1-6) (Burt et al., 1995b). More-over, data from a 10-year follow-up of most of the NHANES I population showed that the incidence of hypertension among black men and women was twice that found among white men and women (Cornoni-Huntley et al., 1989). As described by Gillum (1996), death related to hypertension is more common in black men than in white men. Fortunately, the data from NHANES III show equally good control of hypertension in blacks as in the total population in the United States. Hypertension in blacks is covered in more detail in Chapter 4.

Hispanics

According to data from NHANES III, the age-adjusted prevalence of hypertension is similar in Mexican-Americans and in whites (Burt et al., 1995a). Unfortunately, the percentage of well-controlled Hispanic hypertensives was only 14%, lower by 11% than that for whites and blacks. However, as seen in the ongoing Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial, when given access to care, Hispanics respond to treatment as well as do non-Hispanics (Margolis et al., 2001).

Asian Americans and Pacific Islander–Americans

In various surveys of Asians and Pacific Islanders living in the United States, the prevalence of hypertension has generally been similar to or lower than that in whites (Havas and Sherwin, 1996).

Native Americans

Hypertension has become considerably more common among Native Americans since 1950 or so and is now as common in many Native American groups as in

whites (Acton et al., 1996). Rates of cardiovascular disease are even higher in Native Americans than in whites (Howard et al., 1999).

Populations Outside the United States

Most surveys of people in industrialized countries show that the prevalence of hypertension is similar to that in the U.S. white population, whereas most surveys in less developed countries find a lower prevalence (Seedat, 2000; Ueshima et al., 2000).

Rather marked differences in the prevalence of hypertension among similar populations that cannot be easily explained have also been noted. For example, Shaper et al. (1988) reported a threefold variation among 7,735 middle-aged men in 24 towns throughout Great Britain, with higher rates in northern England and Scotland. Some of the variation could be explained by such obvious factors as body weight or alcohol and sodium and potassium intake, but most of the variation remains unexplained (Bruce et al., 1993).

Equally striking are the major differences in mortality due to coronary disease as related to levels of BP in various countries (van den Hoogen et al., 2000). Rates of CHD mortality at any level of BP were more than three times higher in the United States and northern Europe than in Japan and southern Europe; however, the relative increase in CHD mortality for a given increase in BP is similar in all countries.

INCIDENCE OF HYPERTENSION

Much less is known about the incidence of newly developed hypertension than about its prevalence. The Framingham study provides one database (Kannel et al., 1993; Vasan et al., 2001) and the National Health Epidemiologic Follow-up Study another (Cornoni-Huntley et al., 1989). In the latter study, 14,407 participants in NHANES I (1971–1975) were followed up for an average of 9.5 years. Unfortunately, BP was measured only once for each participant at the beginning of the study, and only the first of three measurements during follow-up was used in the analysis to provide comparability. Therefore, the rates provided by this survey are likely considerably higher than would be found with a more careful assessment based on several readings.

Nonetheless, as seen in Figure 1-8, comparison of the incidence of hypertension (systolic BP, ³160 mm Hg; diastolic BP, ³95 mm Hg) in white men and women shows an approximate 5% increase for each 10-year interval of age at baseline, except in the 65- to 74-year-old group. The incidence among blacks was at least twice that among whites. The high incidence in the 55- to 64-year-old and 65- to 74-year-old groups likely represents a considerable proportion of cases of ISH, because the diagnosis was based on elevations in either systolic or diastolic BP.

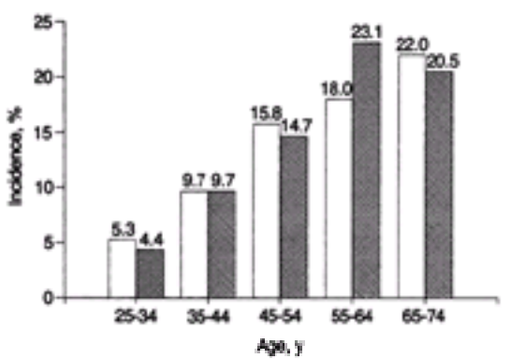

FIG. 1-8. Incidence of hypertension in white men (open bars) and women (cross-hatched bars). Follow-up averaged 9.5 years. (From Cornoni-Huntley J, LaCroix AZ, Havlik RJ. Race and sex differentials in the impact of hypertension in the United States. The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Arch Intern Med 1989;149: 780–788, with permission.)

As seen in Table 1-5, the incidence of hypertension in the Framingham cohort was directly related to the prior level of BP and to age (Vasan et al., 2000).

Blood pressure category	Percentage of 4-yr progression to hypertension (95% confidence intervals)			
	Men, age 35–64 yr	Men, age 65–74 yr	Women, age 35–64 yr	Women, age 65–94 yr
Optimal (SBP <120 mm Hg and DBP <80 mm Hg)	5 (4–6)	15 (12–20)	5 (4–6)	16 (13–21)
Normal (SBP <130 mm Hg and DBP <85 mm Hg)	18 (15–20)	25 (20–31)	12 (10–13)	26 (21–31)
High-normal (SBP 130–139 mm Hg or DBP 85–89 mm Hg)	37 (33–41)	47 (41–54)	37 (33–42)	49 (43–55)

DBP, diastolic blood pressure; SBP, systolic blood pressure.
Data from Vasan RS, Larson MG, Kannel WB, Levy D. Evolution of hypertension from non-hypertensive blood pressure levels. J Am Coll Cardiol 2000;35:2282(abstr).

TABLE 1-5. *Rates of progression to hypertension in Framingham*

CAUSES OF HYPERTENSION

The list of causes of hypertension (Table 1-6) is quite long; however, the cause of more than 90% of the cases of hypertension is unknown (i.e., primary or essential). The proportion of cases secondary to some identifiable mechanism has been debated considerably, as more specific causes have been recognized. Claims that one cause or another is responsible for up to 20% of all cases of hypertension repeatedly appear from investigators who are particularly interested in a certain category of hypertension and therefore see only a highly selected population.

Systolic and diastolic hypertension	Foods containing tyramine and monamine oxidase inhibitors
Primary, essential, or idiopathic	Coarctation of the aorta and aortitis
Identifiable causes	Pregnancy-induced
Renal	Neurologic disorders
Renal parenchymal disease	Increased intracranial pressure
Acute glomerulonephritis	Sleep apnea
Chronic nephritis	Quadriplegia
Polycystic disease	Acute porphyria
Diabetic nephropathy	Familial dysautonomia
Hydronephrosis	Lead poisoning
Renovascular disease	Guillain-Barré syndrome
Renal artery stenosis	Acute stress (including surgery)
Other causes of renal ischemia	Psychogenic hypertension
Renin-producing tumors	Hypoglycemics
Renogenic	Burns
Primary sodium retention (Liddle's syndrome, Gordon's syndrome)	Alcohol withdrawal
Endocrine	Sickle cell crisis
Acromegaly	After resuscitation
Hypothyroidism	Perioperative
Hyperthyroidism	Increased intravascular volume
Hypercalcemia (hyperparathyroidism)	Alcohol
Adrenal disorders	Nicotine
Cortical disorders	Cyclosporine, tacrolimus
Cushing's syndrome	Other agents (see Table 16-5)
Primary aldosteronism	**Systolic hypertension**
Congenital adrenal hyperplasia	Increased cardiac output
Medullary tumors (pheochromocytoma)	Aortic valvular insufficiency
Extraadrenal chromaffin tumors	Arteriovenous fistula; patent ductus
11-β-Hydroxysteroid dehydrogenase deficiency or inhibition (licorice)	Thyrotoxicosis
Carcinoids	Paget's disease of bone
Exogenous hormones	Beriberi
Estrogen	Arterial rigidity
Glucocorticoids	
Mineralocorticoids	
Sympathomimetics	
Erythropoietin	

TABLE 1-6. *Types and causes of hypertension*

Data from surveys of various populations are available (Table 1-7). Even though the patients in some of these studies were referred specifically for evaluation for identifiable causes or because they had more severe hypertension wherein identifiable causes are more likely, the prevalence of primary (essential) hypertension was 90% or higher.

Diagnosis	Frequency of diagnosis (%)				
	Gifford, 1969 (n = 4,328)	Berglund et al., 1974 (n = 989)	Rudnick et al., 1977 (n = 665)	Donelson and Diamondstein, 1981 (n = 1,000)	Sinclair et al., 1987 (n = 2,793)
Essential hypertension	89	94	94	96.3	92.1
Chronic renal disease	5	4	5	2.4	5.6
Renovascular disease	4	1	0.2	1.0	0.7
Coarctation of the aorta	1	0.1	0.2	—	—
Primary aldosteronism	0.5	0.1	—	0.1	0.3
Cushing's syndrome	0.2	—	0.2	0.1	0.1
Pheochromocytoma	0.2	—	—	0.2	0.1
Oral contraceptive use	—	—	0.2	0.3	1.0

TABLE 1-7. *Frequency of various diagnoses in hypertensive subjects*

Perhaps the best data on what could be expected in a usual clinical practice come from the study by Rudnick et al. (1977), which involved 655 hypertensive patients in a family practice in Hamilton, Ontario, Canada. Each patient had a complete workup, including an intravenous pyelogram. Notice again the rarity of identifiable hypertension in this relatively unselected population. The proportion of identifiable causes of hypertension does differ in both old and young patients (see Chapter 4 and Chapter 16, respectively).

POPULATION RISK FROM HYPERTENSION

Now that the definition of hypertension and its classification have been provided, along with various estimates of its prevalence, the impact of hypertension on the population at large can be considered. As noted, for the individual patient, the higher the level of BP, the greater the risk of morbidity and mortality. However, for the population at large, the greatest burden from hypertension occurs among people with only minimally elevated pressures, because there are so many of them. This burden can be seen in Figure 1-9, where 12-year cardiovascular mortality rates observed with each increment of BP are plotted against the distribution of the various levels of BP among the 350,000 men aged 35 to 57 years who were screened for the Multiple Risk Factor Intervention Trial (National High Blood Pressure Education Program Working Group, 1993). Although the mortality rates climb progressively, most deaths occur in the much larger proportion of the population with minimally elevated pressures. By multiplying the percentage of men at any given level of BP by the relative risk for that level, it can be seen that more cardiovascular mortality will occur in those with a diastolic BP of 80 to 84 than among those with a diastolic BP of 95 mm Hg or greater.

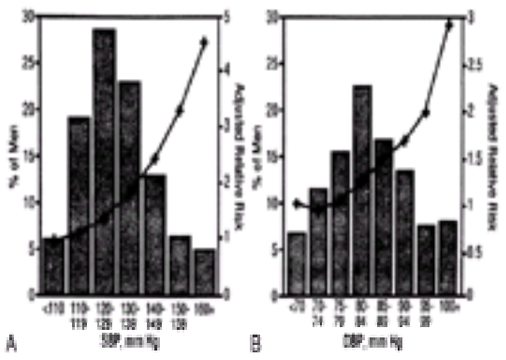

FIG. 1-9. A: Percentage distribution of systolic blood pressure (SBP) for men screened for the Multiple Risk Factor Intervention Trial who were 35 to 57 years old and had no history of myocardial infarction (n = 347,978) (bars) and corresponding 12-year rates of cardiovascular mortality by SBP level adjusted for age, race, total serum cholesterol level, cigarettes smoked per day, reported use of medication for diabetes mellitus, and imputed household income (using census tract for residence) (curve). **B:** Same as part **A**, showing the distribution of diastolic blood pressure (DBP) (n = 356,222). (From National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group report on primary prevention of hypertension. Arch Intern Med 1993;153:186–208, with permission.)

Strategy for the Population

This disproportionate risk for the population at large from relatively mild hypertension bears strongly on the question of how to achieve the greatest reduction in the risks of hypertension. In the past, most efforts have been directed at the group with the highest levels of BP. However, this “high-risk” strategy, as effective as it may be for those affected, does little to reduce total morbidity and mortality if the “low-risk” patients, who make up the largest share of the population at risk, are ignored (Rose, 1985, 1992).

Many more people with mild hypertension are now being treated actively and intensively with antihypertensive drugs. However, as emphasized by Rose (1985, 1992), a more effective strategy would be to lower the BP level of the entire population, as might be accomplished by reduction of sodium intake. Rose estimated that lowering the entire distribution of BP by only 2 to 3 mm Hg would be as effective in reducing the overall risks of hypertension as prescribing current antihypertensive drug therapy for all people with definite hypertension.

This issue is eloquently addressed by Stamler (1998):

> The high-risk strategy of the last 25 years— involving detection, evaluation, and treatment (usually including drug therapy) of tens of millions of people with already established high BP—useful as it has been, has serious limitations: It is late, defensive, mainly reactive, time-consuming, associated with adverse effects (inevitable with drugs, however favorable the mix of benefit and risk), costly, only partially successful, and endless. It offers no possibility of ending the high BP epidemic.
>
> However, present knowledge enables pursuit of the additional goal of the primary prevention of high BP, the solution to the high BP epidemic. For decades, extensive concordant evidence has been amassed by all research disciplines showing that high salt intake, obesity, excess alcohol intake, inadequate potassium intake, and sedentary lifestyle all have adverse effects on population BP levels. This evidence is the solid scientific foundation for the expansion in the strategy to attempt primary prevention of high BP by improving lifestyles across entire populations.

The broader approach is almost certainly correct on epidemiologic grounds. However, until such mass strategies can be implemented, we are left with the need to treat in a better fashion those with established hypertension.

DETECTION AND CONTROL OF HYPERTENSION IN THE POPULATION

As seen in Table 1-1, the percentages of people in the United States who are aware of their hypertension, who are receiving treatment, and whose hypertension is controlled have risen progressively over the last 20 years. However, using the threshold level of 140/90 mm Hg, the percentage of people in the United States with controlled hypertension as of 1994 was only 27.4%. Similarly poor rates of adequate control have been noted worldwide (Cruickshank et al., 2001; Mancia et al.,

1997; Ueshima et al., 2000).

Continued Problems

Obviously, adequate management of the large hypertensive population has proved to be difficult. This difficulty arises from multiple causes. Perhaps the most pervasive is the inherent nature of hypertension: a life-long condition that is usually asymptomatic for many years but that requires daily therapy that may itself induce symptoms. The high prevalence of systolic hypertension in the elderly has not been appreciated (Franklin et al., 2001a), and most therapy has been directed against diastolic elevations so that systolic BP seldom is controlled (Swales, 1999).

Another factor is the inadequate health care provided to many of the poor in the United States, a group that includes a large proportion of blacks, in whom the prevalence of hypertension is highest and the largest percentage of uncontrolled disease is present (Shea et al., 1992). Even with Medicare coverage of costs, indigent blacks do not obtain the same levels of health care as do indigent whites (Gornick et al., 1996), so that outreach programs clearly are needed.

The continued difficulties in maintaining adequate follow-up and treatment of the poor are not by any means unique to the United States. Similar problems have been noted in England, where a nationalized health care system should help the poor overcome the economic impediments to adequate BP management (Aylett et al., 1996). In less developed countries, even greater problems, including inadequate funds for medications, continue to impede attempts to control hypertension (Seedat, 2000).

Proposed Solutions

The major need now is not to screen or evaluate but to improve continuation of treatment by maintaining contact and encouraging follow-up care. Improvements in long-term management can be made by both large-scale approaches and individual providers (Yano et al., 1995). Examples of successful large-scale approaches are

- The North Karelia, Finland, control program, which includes intensive community education, hypertension dispensaries run by specially trained nurses, and widespread use of both non-drug and drug therapies (Nissinen et al., 1992)
- Neighborhood health centers with a community-oriented primary care philosophy (Pavlik et al., 1996)
- Work-site facilities for follow-up care (Gomel et al., 1993)
- Outpatient hypertension clinics staffed largely by nonphysicians (Schultz and Sheps, 1994)

In their review of multiple programs designed to enhance the quality and economy of primary care, Yano et al. (1995) noted improvements with certain maneuvers, including computerized reminders, telephone follow-up, nurse implementation of prevention protocols, and multidisciplinary teams. Home BP monitoring has been found to improve the management of hypertension while also reducing the costs (Soghikian et al., 1992). Additional ways to improve maintenance of therapy are provided in Chapter 7.

Benefits of Improved Control of Hypertension

At least partly as a result of the improved control of hypertension, there has been a steady decrease in the mortality rate of CHD and an even greater decrease in that of stroke in the United States since 1972 (Fig. 1-10). The decline in mortality due to these two diseases has been steeper than for noncardiovascular disease and has been observed in men and women, blacks and whites.

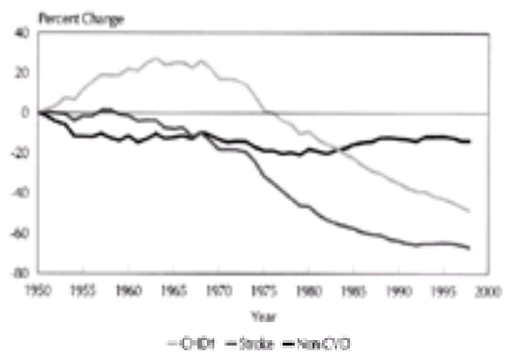

FIG. 1-10. Changes in age-adjusted U.S. death rates from 1950 to 1998. The coronary heart disease (CHD) death rate increased 27% from its level in 1950 to a peak in 1963. By 1998, it was 49% lower than in 1950. The rate for stroke declined in most years, so that by 1998 it was 67% lower than in 1950. The death rate for the noncardiovascular disease (non-CVD) causes of death was only 14% lower in 1998 than in 1950. [Reprinted from NHLBI Chart Book. Cardiovascular diseases. 2000(May):21, with permission.]

The explanation for the reduced mortality rate of cardiovascular disease in the United States remains uncertain. However, the total contribution from all improvements in risk factors, including the control of hypertension, appears to explain about half of the decline. In the Framingham Heart Study, the decline in cardiovascular disease mortality noted in groups of subjects who were 50 to 59 years old in 1950, 1960, or 1970 over the subsequent 20-year intervals was 59% between the female cohorts and 53% between the male cohorts (Sytkowski et al., 1996a). More than half of the decline in CHD mortality in women and from one-third to one-half of the decline in men could be attributed to improvements in risk factors, including reductions in hypercholesterolemia, smoking, and hypertension. The effect of the treatment of hypertension was an important part of the overall reduction in risk, with a 60% reduction in the 10-year risk of mortality from cardiovascular diseases in patients with hypertension who were treated as compared to those who were not treated (Sytkowski et al., 1996b).

With a computer simulation model of the entire U.S. population between the ages of 35 and 84, Hunink et al. (1997) devised these estimates of the reasons for the decline in CHD mortality from 1980 to 1990: 43% by improvements in treatment (e.g., bypass surgery) in patients with CHD; 29% by reduction of risk factors, including smoking, hypercholesterolemia, and hypertension, in patients with CHD; and 25% by primary prevention of these risk factors in people without preexisting CHD. Thus, the overall contribution of reductions in risk factors was slightly more than 50%.

Although a lesser impact of changes in risk factors has been seen in some populations (Kuulasmaa et al., 2000), estimates almost identical to those of Hunink et al. have been presented for the decline in CHD mortality in Scotland between 1975 and 1994 (Capewell et al., 1999).

Because stroke is even more closely related to hypertension than is CHD and, as is delineated in Chapter 5, as greater reductions in stroke mortality than in CHD mortality have been observed in the multiple randomized controlled trials of hypertension treatment, the even greater fall in stroke mortality—67%—seen in the United States from 1950 is logically related to the improved control of hypertension. How-ever, the data are not entirely consistent: Among the residents of Rochester, Minnesota, the incidence rate of stroke was higher in 1990 than in the 1960s and 1970s (Brown et al., 1996). Similarly, according to an analysis of data from NHANES I, II, and III, the prevalence of stroke increased by 7.5% for each 5-year period from 1971 to 1994, whereas the number of stroke survivors increased from 1.5 to 2.4 million people (Muntner et al., 2001). The large number of strokes could be explained by other factors such as better detection of milder stroke cases by improved radiologic imaging, but primary prevention does not seem to have been effective. Nonetheless, when all factors are taken into account, the improved treatment of hypertension has been credited with approximately one-half of the reduction of stroke mortality seen among white women older than 50 and two-thirds of the reduction among black women (JNC, 1997).

These striking decreases in cardiovascular mortality obviously contribute to the increased longevity of the U.S. population. Equally impressive has been the decline in chronic disability in the elderly U.S. population, from 24.9% in 1982 to 21.3% in 1994 (Manton et al., 1997), which must surely reflect the decrease in disabling strokes and heart attacks.

As impressive as these changes are, the United States continues to rank eighteenth of 33 industrialized countries in CHD mortality in men and fourteenth of 33 in

women (Oparil, 1995). Moreover, we should not lose sight of the continued increase in the incidence of two major hypertension-related problems: congestive heart failure and end-stage renal disease (JNC, 1997). Therefore, we have a long way to go in reducing hypertension-related morbidity and mortality.

POTENTIAL FOR PREVENTION

A greater awareness of the causes and accelerators of hypertension may provide insights into the real goal: prevention. Despite more intensive treatment of millions of people with hypertension, we have done little to prevent its onset. The incidence of hypertension in the Framing-ham population has remained quite stable over 30 years (Kannel et al., 1993).

Increasingly strong evidence documents the ability to delay, if not to prevent, the onset of hypertension (He et al., 2000). Crucial to that effort is the prevention of obesity, because in the Framingham population, 70% of hypertension in men and 61% in women was directly attributable to excess adiposity (Kannel, 2000). Unfortunately, the prevalence of obesity in the United States has risen progressively both in adults and, even more disturbingly, in children, among whom more obesity-related hypertension has also been noted (Mokdad et al., 2001). We should keep the goal of prevention in mind as we consider the overall problems of hypertension for the individual patient in the ensuing chapters.

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2
Measurement of Blood Pressure

Now that some of the major issues about hypertension in the population at large have been addressed, we turn to the evaluation of the individual patient with hypertension. This chapter covers the measurement of blood pressure (BP), first considering many aspects of its variability. These, in turn, are involved in a number of special features that are of considerable clinical importance including the “white-coat” effect, nocturnal dipping, and the early morning surge in pressure.

For almost all of the last 100 years since indirect BP measurements have been feasible, they have been hoarded in physicians' offices and held to be highly accurate, capable of definitively diagnosing hypertension by even one determination. Over the past few years, BP has become recognized as a continuous variable, impossible to characterize except by multiple readings under various conditions; its measurement is known to be often inaccurate and in need of escaping the physician's office to be fully effective as a tool for the control of hypertension. In the words of one of its leading students, “Blood pressure measurement is changing” (O'Brien, 2001).

VARIABILITY OF BLOOD PRESSURE

The variability of the BP on repeated measurements, both at a single visit and on separate occasions, is much greater than most practitioners realize (Klungel et al., 2000; Reeves, 1995). Considering the degree of variability found between single measurements made on different occasions, Perry and Miller (1992) concluded:

> Perhaps only one-third to two-thirds of people whose measured diastolic pressures exceed 95 mm Hg actually have average pressures that high…. In a general population, single measurements of diastolic pressure exceed 95 mm Hg in approximately equal numbers of normotensive, borderline and hypertensive patients; moreover, one-third of those who are usually in the hypertensive range are not identified.

By Bayesian analysis, the predictive value of the average of two diastolic BP readings above 90 for the presence of “true” diastolic BP above 90 is only 52% (Schechter and Adler, 1988). If the average of eight readings is above 90, the sensitivity or positive predictive value goes up, but only to 73%.

The adverse consequences of not recognizing and dealing with this variability are obvious: Individual patients may be falsely labeled as hypertensive or normotensive. If falsely labeled as normotensive, needed therapy may be denied. If falsely labeled as hypertensive, the label itself may provoke ill effects, as noted in Chapter 1, and unnecessary therapy will likely be given.

The typical variability of the BP through the 24-hour day is easily recognized by ambulatory BP monitoring (ABPM) (Fig. 2-1). This printout of readings taken in a single patient every 15 minutes during the day and every 30 minutes at night displays the large differences in daytime readings, the typical dipping during sleep, and the abrupt increase on arising.

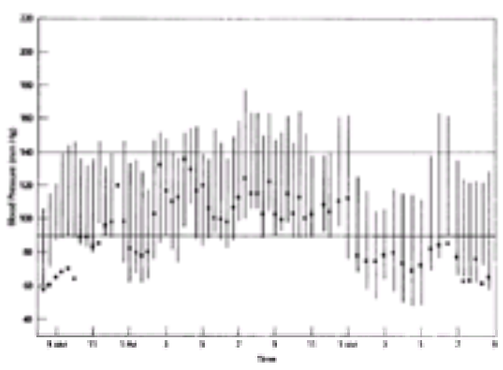

FIG. 2-1. Computer printout of blood pressures obtained by ambulatory blood pressure monitoring over 24 hours, beginning at 9 a.m., in a 50-year-old man with hypertension receiving no therapy. The patient slept from midnight until 6 a.m. Solid circles, heart rate in beats per minute. (From Zachariah PK, Sheps SG, Smith RL. Defining the roles of home and ambulatory monitoring. *Diagnosis* 1988;10: 39–50, with permission.)

Sources of Variation

BP readings are often variable because of problems involving the observer (measurement variation) or factors working within the patient (biologic variation) (Beevers et al., 2001a).

Measurement Variations

An impressively long list of factors that can affect the immediate accuracy of office measurements has been compiled and referenced by Reeves (1995) (Table 2-1). These errors are more common than most realize and regular, frequent retraining of personnel is needed to prevent them (Grim and Grim, 1995).

TABLE 2-1. *Factors affecting the immediate accuracy of office blood pressure (BP) measurements*

Biologic Variations

Biologic variations in BP may be either random or systematic. Random variations are uncontrollable but can be reduced simply by repeating the measurement as many times as needed. Systematic variations are introduced by something affecting the patient and, if recognized, are controllable; however, if not recognized, they cannot be reduced by multiple readings. An example is a systematic variation related to environmental temperature: Higher readings usually are noted in the winter, particularly in thin people, who often display systolic BPs 10 mm Hg or higher than they do in the summer (Kristal-Boneh et al., 1996).

As seen in Figure 2-1, considerable differences in readings can be seen at different times of the day, whether or not the subject is active (Schwartz et al., 2000). Beyond these, between-visit variations in BP can be substantial. Even after three office visits, the standard deviation of the difference in BP from one visit to another in 32 subjects was 10.4 mm Hg for systolic BP and 7.0 mm Hg for diastolic BP (Watson et al., 1987).

Types of Variation

Variability in BP arises from different sources: short-term, daytime, diurnal, and seasonal (Pickering, 1999a). *Short-term* variability at rest is affected by respiration and heart rate, which are under the influence of the autonomic nervous system. *Daytime* variability is mainly determined by the degree of mental and physical activity. *Diurnal* variability is substantial, with an average fall in BP of approximately 15% during sleep. As noted, *seasonal* variations can be considerable.

The overriding influence of activity on day-time and diurnal variations was well demonstrated in a study of 461 untreated hypertensive patients whose BP was recorded with a portable noninvasive device every 15 minutes during the day and every 30 minutes at night over 24 hours (Clark et al., 1987). In addition, five readings were taken in the clinic before and another five after the 24-hour recording. When the mean diastolic BP readings for each hour were plotted against each patient's mean clinic diastolic BP, considerable variations were noted, with the lowest BPs occurring during the night and the highest near midday (Fig. 2-2A). The patients recorded in a diary the location at which their BP was taken (e.g., at home, work, or other location) and what they were doing at the time, selecting from 15 choices of activity. When the effects of the various combinations of location and activity on the BP were analyzed, variable effects relative to the BP recorded while relaxing were seen (Table 2-2). When the estimated effects of the various combinations of location and activity then were subtracted from the individual readings obtained throughout the 24-hour period, little residual effect related to the time of day was found (Fig. 2-2B). The authors concluded that “there is no important circadian rhythm of BP which is independent of activity” (Clark et al., 1987).

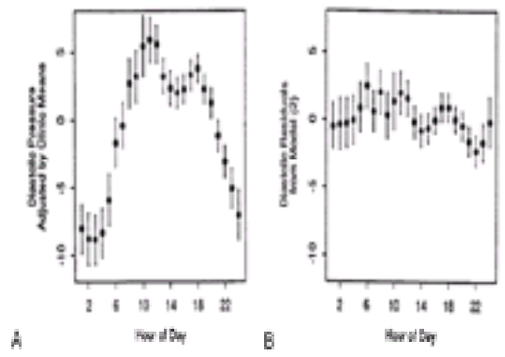

FIG. 2-2. A: Plot of diastolic blood pressure readings adjusted by individual clinic means. **B:** Plot of the diastolic blood pressure hourly mean residuals after adjustments for various activities by a timeof-day model. The hourly means (*solid circles*) ± 2 standard errors of the mean (*vertical lines*) are plotted versus the corresponding time of day. (From Clark LA, Denby L, Pregibon D, et al. A quantitative analysis of the effects of activity and time of day on the diurnal variations of blood pressure. *J Chronic Dis* 1987;40:671–679, with permission.)

Activity	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Meetings	+20.2	+15.0
Work	+16.0	+13.0
Transportation	+14.0	+9.2
Walking	+12.0	+5.5
Dressing	+11.5	+9.5
Chores	+10.7	+8.7
Telephone	+9.5	+7.2
Eating	+8.8	+9.6
Talking	+6.7	+6.7
Desk work	+5.9	+5.3
Reading	+1.9	+2.2
Business (at home)	+1.6	+3.2
Television	+0.3	+1.1
Relaxing	0.0	0.0
Sleeping	−10.0	−7.6

Data adapted from Clark LA, Denby L, Pregibon D, et al. A quantitative analysis of the effects of activity and time of day on the diurnal variations of blood pressure. J Chronic Dis 1987;40:671–679.

TABLE 2-2. *Average changes in blood pressure associated with commonly occurring activities, relative to blood pressure while relaxing*

Additional Sources of Variation

Beyond the level of activity and the stresses related to the measurement, a number of other factors affect BP variability, including the sensitivity of baroreflexes and the level of BP, with more variability occurring with higher BPs (Ragot et al., 2001). This latter relationship probably is responsible for the widespread perception that the elderly have more variable BP. When younger and older hypertensives with comparable BP levels were studied, variability was not consistently related to age (Brennan et al., 1986).

It is important to minimize the changes in BP that arise because of variations within the patient. Even little things can have an impact: both systolic BP and diastolic BP may rise 10 mm Hg with a distended urinary bladder (Fagius and Karhuvaara, 1989) or during ordinary conversation (Le Pailleur et al., 1998).

In addition to the factors listed in Table 2-1 and Table 2-2, higher BPs are noted on the day after sleep deprivation (Tochikubo et al., 1996), during defecation (Littler et al., 1974), during coitus (Mann et al., 1982), and when among strangers rather than family (Spitzer et al., 1992). Those who are more anxious or elated tend to have

higher levels (Jacob et al., 1999). Particularly in the elderly, eating may lower the BP (Fagan et al., 1990). Obviously, almost everything one does can change the BP. The contribution of certain activities to variability of the BP should be acknowledged when BPs are measured (Beevers et al., 2001a).

Smoking

Acutely, the surge of nicotine may cause a rise in both systolic BP and diastolic BP that lasts for 15 to 30 minutes (Groppelli et al., 1992), likely mediated by release of norepinephrine from adrenergic nerves. Even more prolonged elevations in BP follow the use of smokeless tobacco (Hirsch et al., 1992). When their BPs are taken more than 30 minutes after their last cigarette, smokers have generally been found to be no more hypertensive than nonsmokers, and many are often less hypertensive, because smokers tend to weigh less than nonsmokers (Mikkelsen et al., 1997). However, the repeated pressor effects of each cigarette can result in elevated BPs for most of the day in the typical pack-per-day smoker, clearly contributing to the increased risk for cardiovascular diseases noted among smokers.

Caffeine

Caffeine causes an acute rise in BP and levels of both renin and catecholamines after 12 hours of abstinence. Although considerable tolerance develops, some pressor effect may be observed with repeated consumption (see Chapter 3).

Alcohol

Acutely, when 0.75 g per kg body weight of ethanol was consumed by a group of young normotensives in 15 minutes so that the blood alcohol level rose quickly to almost 100 mg per dL, a definite rise in BP occurred (Potter et al., 1986). Chronically, alcohol intake beyond 2 oz per day may induce considerable and persistent rises in BP, so that heavy alcohol intake may be the most common cause of reversible hypertension (see Chapter 3).

Is Variability Harmful?

One last issue about BP variability is whether it is, by itself, harmful. In both cross-sectional (Mancia et al., 2000) and longitudinal (Sander et al., 2000) data, greater BP variability has been found to be associated with more extensive carotid atherosclerosis. Over an average 8.5-year follow-up of 1,542 subjects, a significant increase in cardiovascular mortality was found with increased daytime systolic BP variability noted on ambulatory monitoring (Kikuya et al., 2000). Therefore, it seems likely that the damage induced by hypertension is related not only to the average BP level but also to the magnitude of its variability. Moreover, some of the protective effect of antihypertensive drug therapy may reflect a decrease in BP variability (Frattola et al., 2000).

Blood Pressure during Sleep and on Awakening

Normal Pattern

The usual fall in BP at night is largely the result of sleep and inactivity rather than the time of day (Sternberg et al., 1995). Whereas the nocturnal fall averages approximately 15% in those who are active during the day, it is only about 5% in those who remain in bed for the entire 24 hours (Casiglia et al., 1996).

The nocturnal dip in pressure is normally distributed with no evidence of bimodality in both normotensive and hypertensive people (Staessen et al., 1997a). Therefore, the separation between “dippers” and “nondippers” is, in a sense, artefactual. Instead of defining *non-dipping* as less than a 10% fall in nocturnal BP, as usually is done, Staessen et al. (1997a) recommended that nondipping be defined as a fall of less than the ninety-fifth percentile of that noted in the 4,765 normotensive subjects in their large international database, or –0.3/–1.1 mm Hg. By their definition, therefore, only those who have a nocturnal rise above the daytime level would be classified as nondippers. Despite the scientific purity of this position, multiple data suggest that a looser definition is more appropriate. Nonetheless, the pattern of BP during sleep is highly variable and poorly reproducible, so that classification of dipping status on the basis of a single ambulatory BP recording is unreliable (Manning et al., 2000).

The degree of nocturnal fall tends to decrease with increasing age (Staessen et al., 1997a) or coexisting diabetes, is similar in men and women, and tends to be greater in smokers, who escape the pressor effect of nicotine while they sleep (James et al., 1995). U.S. blacks and Hispanics were found to have a lesser nocturnal fall in BPs than did whites (Hyman et al., 2000). The lesser degree of dipping may reflect diminished chemoand baroreceptor responses during sleep, as noted in a comparison between young normotensive blacks and whites (Crisostomo et al., 1998). In addition, a lesser nocturnal fall has been noted in patients with various identifiable causes of hypertension (Middeke and Schrader, 1994).

The usual falls in BP and heart rate that occur with sleep reflect a decrease in sympathetic nervous tone. In 13 healthy young men, plasma catecholamine levels fell during rapid-eye-movement sleep, whereas awakening immediately increased epinephrine, and subsequent standing induced a marked increase in norepinephrine (Dodt et al., 1997).

What appears to be nondipping may be simply a consequence of getting up to urinate (Perk et al., 2001) or a reflection of obstructive sleep apnea (Pelttari et al., 1998). Moreover, the degree of dipping during sleep is affected by the amount of dietary sodium in those who are salt-sensitive: Sodium loading attenuates these individuals' dipping, whereas sodium reduction restores their dipping status (Higashi et al., 1997; Uzu et al., 1999).

Associations with Nondipping

Even though there is no clear separation between dippers and nondippers in large populations, a number of associations have been noted between a lesser fall than usual in nocturnal BP and greater cardiovascular damage and disease by most investigators, but not by all (Cuspidi et al., 1999). Over an average 5.1-year follow-up of 1,542 subjects, mortality was highest in inverted dippers, followed by nondippers (Ohkubo et al., 1997). Similarly, fatal strokes and cardiac events were more frequent in the 10% of 958 older subjects whose nocturnal BP was higher than their daytime BP (Kario et al., 2000a). Nondippers have also been shown to have more cardiac hypertrophy and diastolic dysfunction (Ferrara et al., 1998), strokes (Phillips et al., 2000) and cognitive dysfunction (van Boxtel et al., 1998), more rapid progression of renal insufficiency (Timio et al., 1995), and a higher frequency and complexity of ventricular arrhythmias (Schillaci et al., 1996), including QT dispersion (Kohno et al., 1998).

Associations with Excessive Dipping

Just as a failure of the BP to fall during sleep may reflect or contribute to cardiovascular damage, there may also be danger from too great a fall in nocturnal BP. Floras (1988) suggested that nocturnal falls in BP could induce myocardial ischemia in hypertensives with left ventricular hypertrophy and impaired coronary vasodilator reserve, contributing to the J-curve of increased coronary events when diastolic BP is lowered below 85 mm Hg (see Chapter 5).

The first objective evidence for this threat from too much dipping was the finding by Kario et al. (1996) that more silent cerebrovascular disease (identified by brain magnetic resonance imaging) was found among extreme dippers who had a greater than 20% fall in nocturnal systolic BP. Subsequently, Kario et al. (2000b), in a 41-month follow-up of 575 elderly hypertensives, found the lowest stroke risk to be at a sleep diastolic BP of 75 mm Hg, with an increased risk below 75 mm Hg that was associated with their intake of antihypertensive drugs. Similarly, in a smaller group of hypertensives with stable coronary artery disease, myocardial ischemia occurred during the night more frequently in untreated nondippers and in treated overdippers (Pierdomenico et al., 1998). These findings serve as a warning against late evening or bedtime dosing of drugs that have a substantial antihypertensive effect in the first few hours after intake.

Early Morning Surge

Even more ominous is the usual abrupt rise in BP that occurs after arising from sleep, whether it be in the early morning (Khoury et al., 1992; Peckova et al., 1998) or after a midafternoon siesta (Bursztyn et al., 1999). As amply described, the early morning hours after 6 a.m. are accompanied by an increased prevalence of all cardiovascular catastrophes as compared to the remainder of the 24-hour period (Muller, 1999). In one group of 137 patients, the onset of the initial symptoms of acute myocardial infarction was carefully ascertained; the most common onset was within the first hour after awakening (Goldberg et al., 1990) (Fig. 2-3). Similar early morning increases have been noted for stroke (Elliott, 1998), cardiac arrest (Soo et al., 2000), rupture of the abdominal aorta (Manfredini et al., 1999), and epistaxis

(Manfredini et al., 2000).

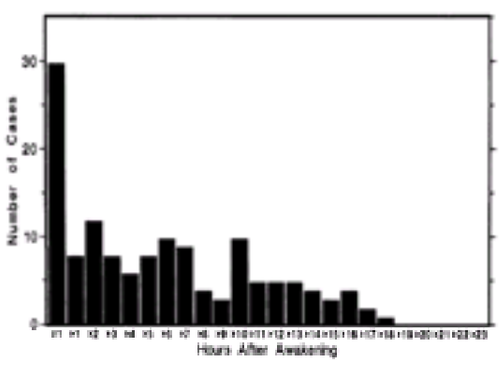

FIG. 2-3. Time of onset of initial symptoms of acute myocardial infarction after awakening in 137 patients. (From Goldberg RJ, Brady P, Muller JE, et al. Time of onset of symptoms of acute myocardial infarction. *Am J Cardiol* 1990;66:140–144, with permission.)

These abrupt changes are likely mediated by heightened sympathetic activity after hours of relative quiescence (Dodt et al., 1997; Panza et al., 1991), which may be accentuated in subjects with a great deal of hostility (Pasic et al., 1998). Beyond the abrupt increase in BP and heart rate, increased platelet aggregability is likely also involved, as confirmed by the protection shown by both b-blockers and aspirin (Johnstone et al., 1996).

Attention must then be directed to ascertaining the degree of the early morning rise in BP and dampening it with appropriate antihypertensive therapy, as is addressed further in Chapter 7.

White-Coat Effect

Actual measurement of the BP may invoke an alerting reaction, a reaction that is only transient in most patients but persistent in some. It usually is seen in people who have a greater rise in BP on standing and during mental stress (Lantelme et al., 1998). This reaction may be partially related to the environment but is mostly related to the measurer.

Environment

There is a hierarchy of alerting: least at home, more in the clinic or office, most in the hospital. Measurements by the same physician were higher in the hospital than in a health center (Enström et al., 2000). Whether taken by the physician or an automatic device, readings obtained in the office were higher than those taken out of the office (Myers et al., 1997).

Measurer

Figure 2-4 demonstrates that the presence of a physician usually causes a rise in BP that is sometimes very impressive (Mancia et al., 1987). The data in Figure 2-4 were obtained from patients who underwent a 24-hour intraarterial recording after 5 to 7 days in the hospital. When the intraarterial readings were stable, the BP was measured in the noncatheterized arm by both a male physician and a female nurse, half of the time by the physician first, the other half by the nurse first. The patients had not met the personnel but had been told that they would be coming. When the physician took the first readings, the BPs rose an average of 22/14 mm Hg and as much as 74 mm Hg systolic. The readings were approximately half that much above baseline at 5 and 10 minutes. Similar rises were seen during three subsequent visits. When the nurses took the first set of readings, the rises were only half as great as those noted by the physician, and the BP usually returned to near-baseline when measured again after 5 and 10 minutes. The rises were not related to patient age, gender, overall BP variability, or BP levels. Similar nurse-physician differences have been repeatedly noted (La Batide-Alanore et al., 2000).

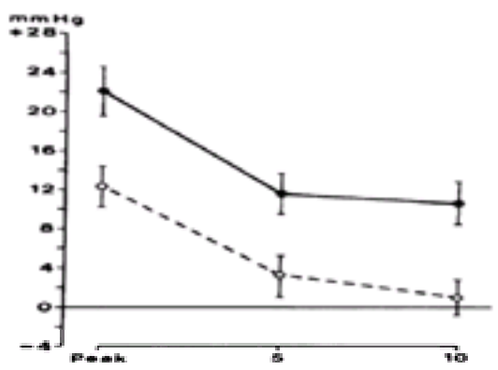

FIG. 2-4. Comparison of maximum (or peak) rises in systolic blood pressure in 30 subjects during visits with a physician (*solid line*) and a nurse (*dashed line*). The rises occurring at 5 and 10 minutes into the visits are shown. Data are expressed as mean (± standard error of the mean) changes from a control value taken 4 minutes before each visit. (Reprinted from Mancia G, Paroti G, Pomidossi G, et al. Alerting reaction and rise in blood pressure during measurement by physician and nurse. *Hypertension* 1987;9: 209–215, with permission.)

These findings are in keeping with a large amount of data that indicates a marked tendency in most patients for BP to fall after repeated measurements, regardless of the time interval between readings (Pickering, 1994). They strongly suggest that nurses and not physicians should measure the BP and that at least three sets of readings should be taken before the patient is labeled hypertensive and the need for treatment is determined.

White-Coat Hypertension

As will be noted, *white-coat hypertension* has been variably defined. The most appropriate definition is an average of multiple daytime out-of-the-office BPs of less than 135/85 mm Hg in the presence of usual office readings above 140/90 mm Hg (O'Brien et al., 2000; Pickering et al., 1999a).

Most patients have higher BP levels when taken in the office than when taken out of the office, as shown in a comparison between the systolic BPs obtained by a physician versus the average day-time systolic BPs obtained by ambulatory monitors (Pickering, 1996) (Fig. 2-5). In the figure, all the points above the diagonal line represent higher office readings than out-of-office readings, indicating that a majority of patients demonstrate the white-coat effect.

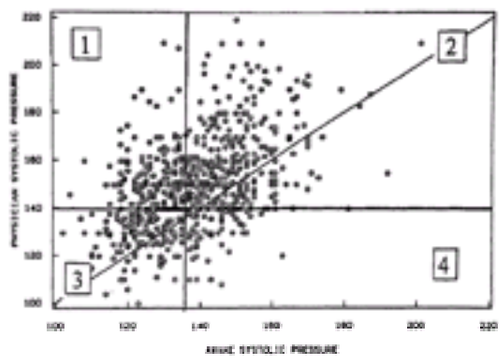

FIG. 2-5. Plot of clinic systolic and daytime ambulatory blood pressure readings in 573 patients. *1*, Patients with white-coat hypertension; *2*, patients with sustained hypertension; *3*, patients with normal blood pressure; *4*, patients whose clinic blood pressure underestimates ambulatory blood pressure. The majority of sustained hypertensives and normotensives had higher clinic pressures than awake ambulatory pressures. (From Pickering TG. Ambulatory monitoring and the definition of hypertension. *J Hypertens* 1992;10:401–409, with permission.)

Whereas most patients exhibiting a white-coat effect also had elevated out-of-office readings, so that they are hypertensive in all settings (Fig. 2-5, group 2), a smaller but significant number of patients had normal readings outside the office—that is, white-coat hypertension (Fig. 2-5, group 1). Pickering et al. (1988) had previously found that among 292 untreated patients with persistently elevated office readings over an average of 6 years, the out-of-office readings recorded by a 24-hour ambulatory monitor were normal in 21%. Since that observation, the prevalence of white-coat hypertension has been found to be approximately 20% in multiple groups of patients with office hypertension (Høegholm et al., 1992; Owens et al., 1999; Staessen et al., 1993; Verdecchia et al., 1995).

To avoid confusion between the white-coat effect and white-coat hypertension, the 1996 World Health Organization Expert Committee report suggests the term *isolated clinic hypertension* to indicate white-coat hypertension, but the latter name will likely stick. As Pickering (1996) emphasized, “White coat hypertension is a measure of blood pressure level, whereas the white coat effect is a measure of change. A large white coat effect is by no means confined to patients with white coat hypertension, and indeed is often more pronounced in patients with severe hypertension.”

Although the white-coat effect is responsible for the existence of white-coat hypertension, no significant correlation was found between the white-coat effect assessed by BP measurements during a clinic visit and the office-daytime ambulatory BP difference that defines white-coat hypertension (Parati et al., 1998).

As interest in white-coat hypertension has grown, a number of its features have become apparent, including

- The prevalence depends largely on the definition of the upper limit of normal for daytime out-of-office readings; depending on the level chosen, the prevalence has been shown to vary from as low as 12% to as high as 53.2% (Verdecchia et al., 1995). Pickering et al. (1988) used 134/90 mm Hg, the ninetieth percentile of the levels obtained in normotensive subjects.
- Verdecchia (2000) concludes that “a correct definition includes an average daytime ambulatory BP of <135 mm Hg systolic and 85 mm Hg diastolic, whereas levels of <130/80 may be defined as optimum.”
- The prevalence of white-coat hypertension may be reduced if the office readings are based on at least five separate visits (Pearce et al., 1992). However, recall that Pickering's original observation involved patients with an average duration of office hypertension of 6 years. The less the elevation in office BP, the greater the frequency of white-coat hypertension (Verdecchia et al., 2001).
- Obviously, only daytime ambulatory readings should be used to define white-coat hypertension, as nighttime readings are typically lower.
- Multiple self-obtained home readings are as good as ambulatory readings to document white-coat hypertension (Stewart et al., 1996).
- The prevalence rises with the age of the patient (Mansoor et al., 1996) and is particularly high in elderly patients with isolated systolic hypertension (Aihara et al., 1998).
- Smokers seem to have a diminished white-coat effect, perhaps because they have a persistent activation of their sympathetic nervous system from the nicotine (Mikkelsen et al., 1997; Verdecchia et al., 2001).
- Women may be more likely to have higher office readings that would engender more white-coat hypertension (Verdecchia et al., 2001), particularly when their BP is measured by a male observer (Millar and Accioly, 1996).
- Some patients considered to have resistant or uncontrolled hypertension on the basis of office readings instead have white-coat hypertension and, therefore, may not need more aggressive therapy (Redon et al., 1998). However, most treated hypertensives with persistently high office readings also have high out-of-office readings so that their inadequate control cannot be attributed to the white-coat effect (Mancia et al., 1997a).
- Antihypertensive therapy has been shown to reduce office BP to the same extent in patients with sustained and white-coat hypertension but lowered the ambulatory BP in only those with sustained hypertension (Pickering et al., 1999a). Therapy reduced the differences between clinic and ambulatory BP, but those changes were not related to regression of left ventricular hypertrophy (Parati et al., 2000).

Beyond these features, two more important and interrelated issues remain: What is the natural history of white-coat hypertension, and what is its prognosis?

Natural History

Too few patients have been followed long enough to be sure of the natural history of white-coat hypertension (Verdecchia, 2001). Whereas Bidlingmeyer et al. (1996) found that 60 of 81 patients had a progression to a daytime ambulatory BP greater than 140/90 mm Hg over a 5- to 6-year follow-up, others have found that only 10% to 30% become hypertensive over 3 to 5 years (Pickering et al., 1999a). Whereas this transition may suggest that white-coat hypertension is a prehypertensive state, it may also reflect regression to the mean, with a fall in the initially high office readings and a rise in the initially low ambulatory values. This explanation is supported by the finding that among 90 patients initially found to have white-coat hypertension, repeated ambulatory monitoring 3 months later revealed higher readings in 52 so that only 38 were still classified as having white-coat hypertension (Palatini et al., 1998).

Prognosis

Uncertainty remains about the risks of white-coat hypertension. Some investigators find that white-coat hypertensives are at relatively little risk when identified and remain so over variable periods of follow-up (Kario et al., 2001; Verdecchia, 2001). Others find considerably more risk. The issue is confounded by the use of totally inaccurate and capricious ascertainment of white-coat hypertension in some surveys (Muscholl et al., 1998). It is hoped that those who investigate and write about this condition will use the criteria now widely accepted: an office reading of 140/90 mm Hg or higher and an average daytime ambulatory reading of less than 135/85 mm Hg (O'Brien et al., 2000; Pickering et al., 1999a).

In their review of the metabolic and biochemical features and extent of target organ damage in white-coat hypertensives, Pickering et al. (1999a) conclude: “Although the bulk of results has supported the view [of a benign prognosis], the data have not been consistent, in some cases perhaps because of failure to match groups according to demographic variables.”

The major determinant of prognosis, of course, is the morbidity and mortality experience of white-coat hypertensives as compared to normotensives and sustained hypertensives. Here again, the data are inadequate to allow certainty, but in four prospective studies of patients with white-coat hypertension, defined with varying criteria, who were followed up for 3 to 9 years, the cardiovascular event rate has been relatively low, intermediate between that seen in normotensive and hypertensive patients (Khattar et al., 1998; Perloff et al., 1991; Redon et al., 1998; Verdecchia et al., 1996).

Of these series, the best evidence now available comes from the continuing follow-up of 1,522 hypertensive subjects for up to 10 years by Verdecchia et al. (1996) (Fig. 2-6). With a conservative definition of white-coat hypertension (i.e., daytime ambulatory BP <130/80 mm Hg), the rate of major cardiovascular morbid events in such patients was 0.67 per 100 patient-years, little beyond what was seen in normotensives but far less than the 2.71 per 100 patient-years rate seen in those with ambulatory hypertension (daytime BP >131/86 mm Hg in women, >136/ 87 mm Hg in men). As seen in Figure 2-6, when a more liberal definition of white-coat hypertension was used—between the more conservative value of less than 130/80 mm Hg and the values shown for ambulatory hypertension—the event rate rose to

1.73 per 100 patient-years, much closer to that seen with ambulatory hypertension.

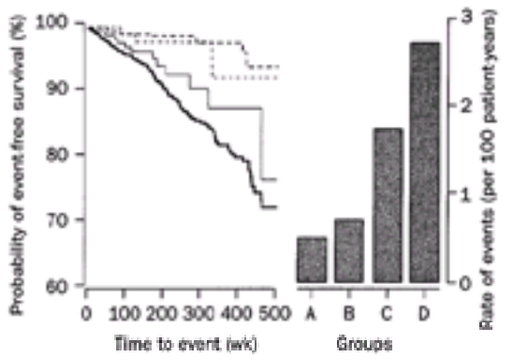

FIG. 2-6. Rate of major cardiovascular morbid events in the normotensive group and in the groups with white-coat and ambulatory hypertension. Event rate did not differ between the normotensive group (*thick dashed line*, group A) and the group with more restrictively defined white-coat hypertension (*thin dashed line*, group B): daytime ambulatory blood pressure, <130/80 mm Hg. Event rate increased in the group with more liberally defined white-coat hypertension (*thin solid line*, group C). The event rate in group C did not differ from that in the group of patients with ambulatory hypertension (*thick solid line*, group D). (From Verdecchia P, Schillaci G, Borgioni C, et al. White-coat hypertension. *Lancet* 1996;348:1444–1445, with permission.)

Verdecchia (2000) concludes his review of the prognosis of white-coat hypertension thus: “On the basis of current evidence, we suggest a temporary verdict of innocent and a treatment based on lifestyle measures in this low-risk stratum of subjects with essential hypertension under the conditions of a correct definition, the absence of important comorbid conditions and adequate follow-up.”

Mainly on the basis of increased degrees of early atherosclerotic target organ damage (Muldoon et al., 2000; Zakopoulos et al., 1999), some predict a higher degree of risk that may warrant more immediate antihypertensive drug therapy (Spence, 1999). At the least, careful follow-up is mandatory.

As should be obvious, the recognition and follow-up of white-coat hypertension are based almost entirely on ABPM (Verdecchia, 2001). As noted later in this chapter, ABPM should be more readily available and used. When it is used, a rational approach for stratification of overall cardiovascular risk can be formulated, taking into account also the dipping status and pulse pressure (Fig. 2-7).

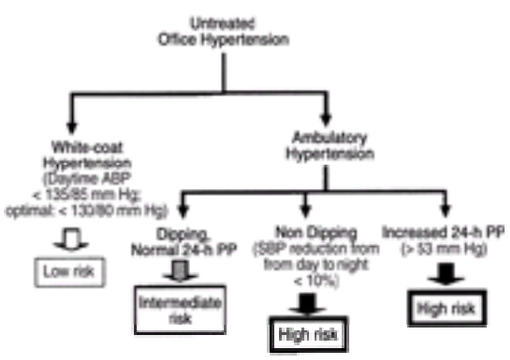

FIG. 2-7. Operational approach for cardiovascular risk stratification on the basis of ambulatory blood pressure (ABP) readings in untreated subjects with essential hypertension. PP, pulse pressure; SBP, systolic blood pressure. (From Verdecchia P. Prognostic value of ambulatory blood pressure. *Hypertension* 2000;35:844–851, with permission.)

White-Coat Normotension

The reverse situation, a normotensive office BP but an elevated ambulatory level, has been termed *white-coat normotension* (Liu et al., 1999). In 61 such patients, left ventricular mass and carotid wall thickness were similar to those seen in patients with sustained hypertension. These patients tended to have greater obesity and high cholesterol levels as compared to those with sustained normotension in and out of the office, and 14 were current smokers. Smokers whose BP is taken in a nonsmoking environment obviously could have a lower BP than that which would be obtained while they are smoking out of the office, which could explain some of the findings. Obviously, more information about this intriguing group of patients is needed.

OFFICE MEASUREMENT OF BLOOD PRESSURE

As Erin O'Brien (2001) has written:

> As we move into the new millennium, the century old Riva-Rocci/Korotkoff technique of measuring blood pressure is changing. There are a number of reasons for this. First, mercury is a toxic substance, the use of which can no longer be countenanced in clinical medicine, and the traditional technique, despite a history of reputable service, is likely to disappear from clinical practice. Second, it is now recognized that though the old technique has given good service, it is fraught with inaccuracies, and accurate automated devices are becoming available to replace the mercury sphygmomanometer. Third, 24 hour ambulatory blood pressure measurement (ABPM) has high-lighted the phenomenon of white coat hypertension, and more reliance is being placed on blood pressure behaviour than on casual measurement of blood pressure levels.

As these changes come about, we must do what can be done to improve current practice (Beevers et al., 2001b). Use of the guidelines shown in Table 2-3 will prevent most measurement errors. Even when properly performed, the measurement of BP indirectly by auscultation of Korotkoff sounds underestimates intraarterial systolic levels by 5 to 8 mm Hg and overestimates diastolic levels by 3 to 7 mm Hg (Fagher et al., 1994).

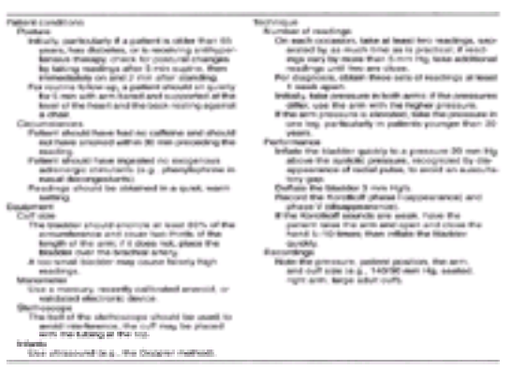

TABLE 2-3. *Guidelines for measurement of blood pressure*

Patient and Arm Position

The patient should be seated comfortably with the arm supported and positioned at the level of the heart (Fig. 2-8). Measurements taken with the arm supported on the armrests of a chair averaged 10 mm Hg higher than those taken with the arm supported in a horizontal position at heart level (Netea et al., 1999). When sitting upright on a table without support, readings may be as much as 10 mm Hg higher because of the isometric exertion needed to support the body and arm (Cushman et al., 1990). Diastolic levels may be higher in the seated position than when supine (Netea et al., 1998).

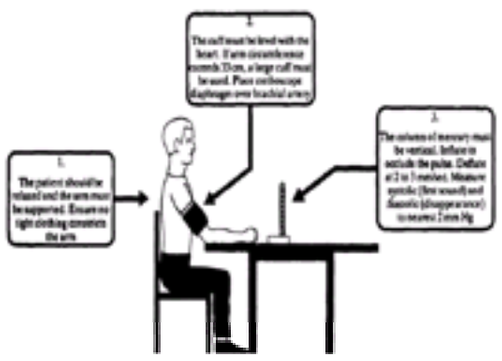

FIG. 2-8. Technique of blood pressure measurement recommended by the British Hypertension Society. (From British Hypertension Society. Standardization of blood pressure measurement. *J Hypertens* 1985;3:293, with permission.)

Differences Between Arms

Initially, the BP should be measured in both arms to ascertain the differences between them (Fotherby et al., 1993); if the reading is higher in one arm, that arm should be used for future measurements. In two series of patients seen in an emergency room, a systolic interarm difference of greater than 10 mm Hg was seen in 39% (Singer and Hollander, 1996) and 15% (Pesola et al., 2001). Although one arm was not more likely to have a higher BP than the other in these studies, other investigators found higher levels in the dominant arm (O'Shea and Murphy, 2000). Lower BP in the left arm is seen in patients with subclavian steal caused by reversal of flow down a vertebral artery distal to an obstructed subclavian artery, as noted in 9% of 500 patients with asymptomatic neck bruits (Bornstein and Norris, 1986). On the other hand, BP may be either higher or lower in the paretic arm of a stroke patient (Dewar et al., 1992).

Standing Pressure

Readings should be taken immediately on standing and after standing at least 2 minutes to check for spontaneous or drug-induced postural changes, particularly in the elderly and in diabetics. In most people, systolic BP falls and diastolic BP rises by a few millimeters of mercury on changing from the supine to the standing position. In the elderly, significant postural falls of 20 mm Hg or more in systolic BP are more common, occurring in approximately 10% of ambulatory people older than 65 years and in more than half of frail nursing-home residents, particularly in those with elevated supine systolic BP (Ooi et al., 1997) (see Chapter 4).

Leg Pressure

If the arm reading is elevated, particularly in a patient younger than 30, the BP should be taken in one leg to rule out coarctation, as described in the next section.

Sphygmomanometer

In a survey of hospitals and physicians' offices in São Paulo, 21% of the mercury sphygmomanometers and more than 50% of the aneroid manometers were inaccurate (Mion and Pierin, 1998).

If mercury manometers are to be phased out because of the toxic potential of mercury spills and with the inaccuracies of aneroid manometers, automated electronic devices will increasingly be used. Meanwhile, attention to the equipment and technique improves the accuracy of the procedure (Beevers et al., 2001b).

Bladder Size

The width of the bladder should be equal to approximately two-thirds the distance from the axilla to the antecubital space; a 12-cm-wide bladder is adequate for most adults. The bladder should be long enough to encircle at least 80% of the arm. Erroneously high readings may occur with use of a bladder that is too short (Aylett et al., 2001) and erroneously low readings with a bladder that is too wide (Bakx et al., 1997).

Most sphygmomanometers sold in the United States have a cuff with a bladder that is 12 cm wide and 23 cm long, which is too short for patients with an arm circumference greater than 28 cm, whether fat or muscular (Aylett et al., 2001). Bakx et al. (1997) recommend the use of one bladder size, 13 cm × 36 cm, for standard use in adults. Children require smaller cuffs depending on their size (Clausen et al., 1999). Meanwhile a triple-bladder cuff (tricuff), which automatically selects the appropriate size in relation to the arm circumference, has been marketed (Stolt et al., 1993).

Cuff Position

If the bladder within the cuff does not completely encircle the arm, particular care should be taken to ensure that the bladder is placed over the brachial artery. The lower edge of the cuff should be approximately 2.5 cm above the antecubital space. In extremely obese people, a thigh cuff may be used with the wide bladder folded on itself, or the bladder may be placed on the fore-arm and the sounds heard over the radial artery.

Manometer

Despite the pleas that they be retained (DW Jones et al., 2001), mercury manometers are being phased out because of concern over toxicity from spills (O'Brien, 2001). At the least, a few should be kept in every facility as standards for other manometers. O'Brien hopes that the replacement of mercury will be accompanied by replacement of the *mm Hg* unit by the International System of Units unit for pressure, the kilopascal, or kPa (1 kPa = 7.5 mm Hg).

Aneroid manometers are less reliable than mercury manometers and easily become inaccurate. They are not suitable replacements for mercury manometers (Jones et al., 2000).

Electronic devices are rapidly taking over the home market and will most likely become standard in offices and hospitals. Fortunately, their accuracy and reliability are improving, and more have passed the protocols of the U.S. Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society (BHS) (O'Brien et al., 2001; Verdecchia, 2001). These include the following models: A&D UA767 and 767PC; Assure A30 and W20; Instromedix QD; Omron 403c, 705CP, 706, 711, 712c, 713c, and 722c; and Terumo ES-H51 (Yarows et al., 2000). In a comparative study against the Omron 712c device, only the Assure A30 model (and the unapproved Sunbeam 7654) gave readings that differed more than the human error of office auscultation (Yarows and Brook, 2000).

Many of the newer electronic devices are based on oscillometry, which detects initial (systolic) and maximal (mean arterial pressure) oscillations in the brachial artery and calculates the diastolic BP based on proprietary algorithms. In general, the readings obtained by auscultatory and oscillometric devices are closely correlated (Yarows et al., 2000). The oscillometric devices are faster to use, and they minimize terminal digit preference wherein the last number is rounded off to 0 or 5. Some of the electronic devices inflate automatically, which is especially useful for patients with arthritis. Others have a printer attached, and some can have the data

downloaded after storing a number of readings. Obviously, the more features a model offers, the more expensive it is. An adequate device can be purchased for less than $40. They can easily be compared for accuracy against a mercury unit (Nash, 1994) and, at the least, should be checked by having the patient use it on one arm while the pressure is simultaneously taken with an office sphygmomanometer on the other arm.

Random-zero manometers have been used to reduce observer bias, but they underestimate the BP (Conroy et al., 1996).

Wrist and Finger Devices

Wrist oscillometric devices, such as the Omron R3 or 605, have provided good accuracy and reproducibility (Watson et al., 1998) but should always be checked against a device with an upper arm cuff (Zweiker et al., 2000).

Finger devices measure the pressure in the finger by volume-clamp plethysmography. The Finapres finger cuff may be used for continuous BP monitoring under carefully controlled conditions (Silke and McAuley, 1998), but it is not suitable for intermittent readings (Lal et al., 1995). Home finger units are not recommended (White et al., 1999).

Automated Devices

Most of the automated oscillometric devices increasingly used in offices, emergency rooms, and hospitals are often inaccurate. Devices such as the Dinamapp 8100 (Park et al., 2001) and the IVAC 4200 (Shuler et al., 1998) usually overestimate BP by 10/5 mm Hg. Nonetheless, these and other automated devices such as the Accutorr and Paramed usually provide readings that are satisfactory for most clinical settings (Lehmann et al., 1998). The Welch Allyn Vital Signs bed-side monitor has been validated (CR Jones et al., 2001).

On the other hand, community-based auto-mated machines may be even more inaccurate, particularly in patients with arm sizes smaller or larger than average (Van Durme et al., 2000). For those who cannot use more accurate (and more easily validated) home devices, readings obtained by such an automated machine are better than nothing, but patients should not be managed solely on the basis of the readings from such machines.

Need for Validation

The aforementioned litany of problems with various BP measuring devices reflects a major problem: These devices may be marketed and used without appropriate validation. Many have not been assessed by AAMI or BHS criteria. As Staessen (2000) states:

> Regulatory organizations should guarantee the accuracy of blood pressure–measuring devices, oversee their independent verification and certification, and provide rules for their distribution and use. Such regulations are equally needed for professional and lay consumers and for clinical practice and medical research. Ultimately, a doctor's or a patient's perception of cardiovascular risk and, consequently, the quality and the duration of life of many people rely on the correct assessment of blood pressure, not only in the medical environment but also at home or under ambulatory conditions.

Technique for Measuring Blood Pressure

As noted in Table 2-3, care should be taken to raise the pressure in the bladder approximately 20 mm Hg above the systolic level, as indicated by disappearance of the radial pulse, because patients may have an auscultatory gap (a temporary disappearance of the sound after it first appears), which is related to increased arterial stiffness (Cavallini et al., 1996).

The measurement may be repeated after as little a span as 15 seconds without significantly affecting accuracy. The cuff should be deflated at a rate of 2 to 4 mm Hg/s; a slower rate causes falsely higher readings (Bos et al., 1992).

Disappearance of the sound (phase V) is a more sensitive and reproducible end point than muffling (phase IV) (de Mey, 1995). In some patients with a hyperkinetic circulation (e.g., anemia), the sounds do not disappear, and the muffled sound is heard well below the expected diastolic BP, sometimes near zero. This phenomenon can also be caused by pressing the stethoscope too firmly against the artery. If arrhythmias are present, additional readings with either auscultatory or oscillometric devices may be required to estimate the average systolic and diastolic BP (Lip et al., 2001).

Pseudohypertension

In some elderly patients with very rigid, calcified arteries, the bladder may not be able to collapse the brachial artery, giving rise to falsely high readings, or pseudohypertension (Spence, 1997). The possibility of pseudohypertension should be suspected in elderly people whose vessels feel rigid; who have little vascular damage in the retina or elsewhere, despite markedly high BP readings; and who suffer inordinate postural symptoms despite cautious therapy. Osler's maneuver, in which the radial pulse remains palpable after the pressure in the balloon has occluded the brachial artery, has little use for identifying the few patients with pseudo-hypertension, because of marked intraobserver and interobserver disagreement (Oliner et al., 1993) and because the maneuver frequently is present in elderly people with normal BP (Wright and Looney, 1997). If one is suspicious, an automatic oscillometric recorder or finger BP measurement should settle the issue (Zweifler and Shahab, 1993), but a direct intraarterial reading may be needed.

Ways to Amplify the Sounds

The loudness and sharpness of the Korotkoff sounds depend in part on the pressure differential between the arteries in the forearm and those beneath the bladder. To increase the differential and thereby increase the loudness of the sounds, either the amount of blood in the forearm can be decreased or the capacity of the vascular bed can be increased. The amount of blood can be decreased by rapidly inflating the bladder, thereby shortening the time when venous out-flow is prevented but arterial inflow continues, or by raising the arm for a few seconds to drain venous blood before inflating the bladder. The vascular bed capacity can be increased by inducing vasodilation through muscular exercise, specifically by having the patient open and close the hand ten times before the observer inflates the bladder. If the sounds are not heard well, the balloon should be emptied and reinflated; otherwise, the vessels will have been partially refilled and the sounds thereby muffled.

Taking Blood Pressure in the Thigh

A large (thigh) cuff should be used to avoid factitiously elevated readings. With the patient lying prone and the leg bent and cradled by the observer, the observer listens with the stethoscope for the Korotkoff sounds in the popliteal fossa. This should be done as part of the initial workup of every young hypertensive, in whom coarctation is more common. Normally, the systolic BP is higher and the diastolic BP a little lower at the knee than in the arm because of the contour of the pulse wave (Hugue et al., 1988).

Taking Blood Pressure in Children

If the child is calm, the same technique that is used with adults should be followed; however, smaller, narrower cuffs must be used (see Chapter 16). Korotkoff phase V is more reliable than phase IV (Penny et al., 1996). If the child is upset, the best procedure may be simply to determine the systolic BP by palpating the radial pulse as the cuff is deflated. In infants, the use of ultrasound techniques is much easier (Laaser and Labarthe, 1986).

Blood Pressure during Exercise

The response of BP during graded exercise has been found to predict the development of hypertension in normotensives (Matthews et al., 1998; Miyai et al., 2000; Singh et al., 1999) and their subsequent mortality from cardiovascular disease (Mundal et al., 1996; Kjeldsen et al., 2001). Different upper limits for a normal response to exercise have been used in various series. Matthews et al. (1998) consider an exaggerated response to be a rise of more than 60 mm Hg in systolic BP at 5 minutes, a rise of more than 70 mm Hg at 10 minutes, or a rise of more than 10 mm Hg in diastolic BP at any time. In various series, such an exaggerated response increases the likelihood of the onset of hypertension from two- to fourfold over the sub-sequent 5 to 10 years as compared with that seen with nonexaggerated responses.

Even a rise in BP of more than 30/15 mm Hg in anticipation of an exercise test has been found to predict the onset of hypertension over the next 4 years (Everson et al., 1996).

Because most who have a supernormal response do not develop hypertension if they are normotensive or cardiovascular mortality if they are hypertensive, exercise tests should not be performed for prognostic purposes. If, however, exercise tests are undertaken for appropriate reasons and the BP response is supernormal, the normotensive patient should be advised to modify his or her lifestyle (including gradual institution of an aerobic exercise program), and the hypertensive patient should be advised to achieve better control of existing hypertension. Hypertensives may have an impaired capacity to exercise (Lim et al., 1996), but they should be advised to continue the effort, because a low level of cardiorespiratory fitness is a strong predictor of future mortality, comparable to smoking (Blair et al., 1998).

Recording of Findings

Regardless of which method is used to measure BP, notation should be made of the conditions so that others can compare the findings or interpret them properly. This is particularly critical in scientific reports, yet many articles about hypertension fail to provide this information. As noted in Chapter 1, the pulse pressure should be calculated from the systolic and diastolic levels, as it gives the most valid prognostic value.

Importance of Office Blood Pressures

Even if all the guidelines listed in Table 2-3 are followed, routine office measurements of BP by sphygmomanometry will continue to show considerable variability. However, before discounting even single casual BP readings, recall that almost all the data on the risks of hypertension described in Chapter 1 are based on only one or a few readings taken in large groups of people. There is no denying that such data have epidemiologic value, but a few casual office readings are usually not sufficient to determine the status of an individual patient. Two actions minimize variability. First, at least two readings should be taken at every visit, as many as needed to obtain a stable level with less than a 5–mm Hg difference; second, at least three and, preferably, more sets of readings, weeks apart, should be taken unless the initial value is so high (e.g., >180/120 mm Hg) that immediate therapy is needed.

The closer the initial and subsequent readings are to 140/90 mm Hg, the more repeated readings are needed to allow determination of a patient's status (Perry and Miller, 1992). Although multiple carefully taken office readings may be as reliable as those taken by ambulatory monitors (Pearce et al., 1992; Reeves, 1995), out-of-office readings provide additional data, both to confirm the diagnosis and, more important, to document the adequacy of therapy. White-coat hypertension can be detected only by out-of-office readings; for almost all hypertensives, they will improve both diagnosis and therapy (Asmar and Zanchetti, 2000; Verdecchia, 2001).

HOME MEASUREMENTS

From the preceding, it is clear that BPs recorded in the hospital or office often are affected by both acute and chronic alerting reactions that tend to accentuate variability and raise the BP, giving rise to a significant white-coat effect. Two techniques—home measurements and ABPM—minimize these problems. Whereas ABPM will likely continue to have more limited applications, the use of home measurements will likely continue to expand (Table 2-4): In Heidelberg, Germany, 70% of hypertensives are using the procedure (Krecke et al., 1996). Home measurements are being increasingly accepted in the United States as well (Yarows et al., 2000).

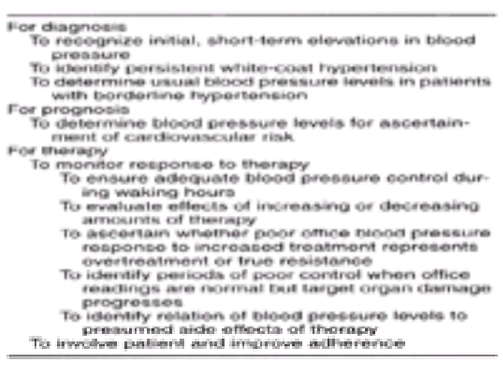

TABLE 2-4. *Indications for home blood pressure monitoring*

The sixth Joint National Committee (1997) report states

> Measurement of blood pressure outside the physician's office may provide valuable information for the initial evaluation of hypertensive patients and for monitoring the response to treatment. Self-measurement has four gen eral advantages: (1) distinguishing sustained from “white-coat hypertension”; (2) assessing the response to antihypertensive medication; (3) improving patient adherence to treatment; and (4) potentially reducing costs.

Except for the additional information provided by measurements taken during sleep and the inability of a few patients to measure their own BP, self-recorded home measurements give almost all the information provided by 24-hour ABPM (Asmar and Zanchetti, 2000). The aver-age BP levels obtained by multiple home readings and those recorded by an ambulatory monitor while the patient is awake are quite close and considerably lower than office readings (Yarows et al., 2000). The self-recorded levels are almost always higher than the full 24-hour ambulatory average, because the latter reading includes the pressures taken during sleep, which are almost always lower.

Concerns have arisen about the reliability of both the performance and the reporting of home BP measurements. In multiple small groups of patients, unaware that their readings were being stored electronically for later surveillance, the self-recorded values have been found to differ by more than 10 mm Hg from the actual measurement in 15% to 25% of the readings (Johnson et al., 1999; Mengden et al., 1998; Myers, 1998; Nordmann et al., 1999). It should be noted that similar or worse inaccuracies in reporting home blood glucose measurements have long been recognized without diminishing its acceptance as a critical element in the management of diabetes (Mazze et al., 1984). Nonetheless, the problem will be increasingly minimized by teletransmission of automatically stored readings to a computer monitor, making them available to the physician as needed (Pickering et al., 1999b; Roth et al., 1999).

Uses for Home Measurements

Diagnosis

Multiple home recordings overcome much of the error caused by the acute and persistent alerting reaction that is responsible for most white-coat hypertension (Hozawa et al., 2001) and can be used to make the diagnosis of hypertension as efficiently as can ambulatory monitoring (Stewart et al., 1996). The data in Table 2-5 document the significantly lower average of the 32 home readings per patient obtained during the 2 weeks between the first and second clinic visits of 268 patients having a BP above 160/95 mm Hg on three consecutive occasions before the first clinic reading (Hall et al., 1990). The home readings were lower in 80% of the patients, by more than 20/10 mm Hg in 40%, so that therapy was deemed unnecessary in 38% of untreated patients and reducible in 16% of treated patients. The accuracy of the home readings taken with the electronic devices is evident by the identical readings taken with that device and the mercury sphygmomanometer at the second clinic visit.

Patient group	First clinic reading (mercury manometer)		Home series (electronic device)		Second clinic reading			
					Electronic device		Mercury manometer	
	SBP (mm Hg)	DBP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)
Untreated (n = 114)	174	103	148	90	165	96	164	97
Treated (n = 154)	177	104	147	87	163	96	164	95

DBP, diastolic blood pressure; SBP, systolic blood pressure.
Data from Hoi CL, Higgs CMB, Notarianni L. Home blood pressure recording in mild hypertension. J Hum Hypertens 1990;4:501–507.

TABLE 2-5. *Blood pressure recorded at home between clinic visits*

From multiple surveys of large populations, a reasonable upper limit of normal for home BP would be 135/85 mm Hg (Thijs et al., 1998; Tsuji et al., 1997).

Prognosis

Few data exist to document the validity of self-recorded home measurements for ascertainment of long-term prognosis except for multiple publications from an ongoing follow-up of 1,913 subjects in Ohasama, Japan. After a mean follow-up of 8.6 years, the risks of cardiovascular mortality have been documented for isolated systolic and combined systolic-diastolic hypertension diagnosed by home measurements (Hozawa et al., 2000). In addition, home readings have been found to be closely correlated to the presence of left ventricular hypertrophy and albuminuria (Jula et al., 1999) and to the progression of diabetic nephropathy (Rave et al., 1999). In all of these studies, home readings have been more closely correlated to target organ damage or prognosis than office readings (Ohkubo et al., 1998). Similarly, home readings are both reproducible over time and predictive of subsequent BP trends (Nesbitt et al., 1997).

Therapy

Home recordings should be used to monitor therapy. When patients are followed only by infrequent office visits, their responses may be either underestimated by the white-coat effect or over-estimated when the BP is taken near the peak of the effect of medications. As a consequence, they may be either overtreated or undertreated.

The problem of overtreatment is encountered occasionally with patients whose office readings do not seem to be responding to increasing therapy but whose out-of-office readings are well controlled (pseudoresistance) (Redon et al., 1998). Other patients who seem properly controlled in the office may have too low pressures at home, a particular danger for the elderly, who may not be able to withstand such low BPs (Raccaud et al., 1992).

When only office readings are taken, the problem of undertreatment may be even more of a danger. The effect of the medication will likely be at its peak within 4 to 6 hours after intake (Elliott, 1996) (Fig. 2-9). However, the effect may not last through a 24-hour period, thus exposing the patient to the dangers of the early morning surge in BP that has been noted to be involved in the higher incidence of cardiovascular catastrophes at that time. The only way to be sure that a patient is properly covered is to measure the BP at the end of the dosing interval. It is possible to have patients come to the office early in the morning before they have taken the day's medication, but it is far easier to have patients take their own BP in the early morning.

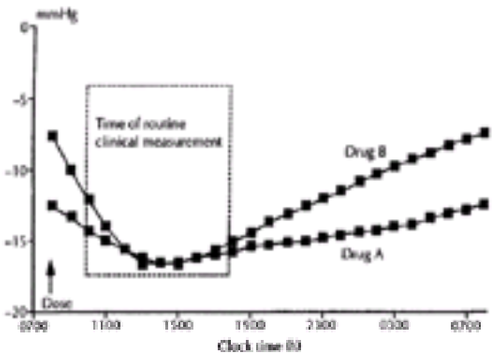

FIG. 2-9. Differential blood pressure reduction profiles over 24 hours, showing different trough-peak (T/P) ratios. Both drugs have peak effects during hours of routine clinical measurement; Drug A, with a T/P ratio of 75%, maintains most of its effect throughout the 24 hours, but drug B, with a T/P ratio of 45%, loses most of its effect overnight. [From Elliott HL. Benefits of twenty-four-hour blood pressure control. *J Hypertens* 1996;14(Suppl 4):S15–S19, with permission.]

Moreover, those who perform home measurements are more likely to remain under management (Elliott, 1995) while reducing the cost of their care (Soghikian et al., 1992; Zamke et al., 2000). In the study by Soghikian et al. (1992), half of 430 patients in a managed-care program were randomly assigned to home measurements, returning their readings by mail, while the other half continued their office-based care. During 1 year, the total costs to the program were 29% less for the home care group (despite the cost of the home device), and those patients had achieved better control of their hypertension.

Series of home readings are a reliable alternative to ABPM both in diagnosis and long-term management of hypertension in general practice (Aylett et al., 1999; Brueren et al., 1998). They minimize the number of subjects needed to assess the efficacy of antihypertensive therapy in comparative trials (Imai et al., 2001) and are easier to use for such studies than are ambulatory monitors (Ragot et al., 2000).

Equipment and Technique

Equipment

As previously noted, reliable and inexpensive electronic home BP devices are increasingly available. Patients should be advised to purchase only those units that have passed the evaluation by AAMI or BHS criteria (O'Brien et al., 2001). For those patients with large arms, large cuffs can be obtained for some of the units. For more money, devices that automatically inflate and print out or store the readings are available.

Technique

All the instructions concerning posture, circumstances surrounding the measurement, and the like that are needed for office readings (Table 2-3) must be followed with home readings as well, and patients should always be given instructions to supplement those provided with the device. The accuracy of the device and the procedure used by the patient (or person taking the home readings) should be checked by a simultaneous measurement on the other arm in the office with a mercury manometer. These points should be made to the patient:

- The first few readings may reflect an alerting reaction similar to that usually experienced in the physician's office. Most patients over-come this anxiety and can obtain “non-stressed” readings after a few days (Celis et al., 1997). However, a few people continue to be frightened by the prospect of finding a high reading that could reflect impending doom, further raising their home readings. If such anxiety cannot be allayed, the patient should not take home measurements.
- Do not be concerned by fluctuations of even 20 mm Hg, but do inform the physician's office if the pressures are going up progressively over a period of 1 week

or longer.

- If the home readings are being taken to determine the average BP for diagnostic purposes, the readings should be made at different times (e.g., when the patient is either relaxed or stressed, anytime throughout the day or evening). It is not appropriate to use a few “relaxed” BP readings that are lower than office readings to diagnose white-coat hypertension (Stergiou et al., 2000). The difficulty of identifying stress-related rises in BP by home readings makes ABPM a more certain way to make the diagnosis.
- If the readings are being taken to determine the adequacy of antihypertensive therapy, they should be taken each day at the same time of day, preferably in the early morning soon after the patient arises from bed, to ensure 24-hour control with the regimen being prescribed. Readings should occasionally be taken repeatedly throughout the interval of a dose of therapy to ascertain both the peak effect and the duration of effect.

AMBULATORY MONITORING

Although some of the same information provided by noninvasive ABPM may be obtained by multiple office readings (Fagard et al., 1997) or home measurements (Stewart et al., 1996), ABPM is being advocated for additional reasons, including more immediate ascertainment of the usual level of BP and for recognition of the prognostic and therapeutic importance of BP during sleep (O'Brien et al., 2000) (Table 2-6). Although the clinical application of ABPM has been markedly restrained in the United States because most third-party payers will not pay for it, the procedure now is being more widely recommended and used in all developed countries. It is hoped that the recent formal request to the U.S. Health Care Financing Administration will lead to financial coverage of the procedure in appropriate circumstances. Not only is it clinically helpful, but ABPM has been shown to be cost effective when used appropriately (Krakoff, 1993). However, as stated by the Joint National Committee (1997), “Ambulatory blood pressure monitoring should not be used indiscriminately as in the routine evaluation of patients with suspected hypertension.”

Situations wherein ABPM is helpful
Excluding white-coat hypertension in patients with office hypertension but no target organ damage
Diagnosing borderline hypertension
Deciding on treatment of elderly patients
Identifying nocturnal hypertension
Assessing apparent resistance to therapy
Assuring efficacy of treatment over entire 24 hours
Managing hypertension during pregnancy
Evaluating hypotension and episodic hypertension
Situations wherein repeat ABPM should be considered
Follow-up of patients found to have white-coat hypertension
Assessment of apparent resistance to appropriate therapy
After major changes in drug therapy
Follow-up of patients with nocturnal hypertension after appropriate therapy
Evaluation of hypotension

ABPM, ambulatory blood pressure monitoring.
Data from O'Brien E, Coats A, Owens P, et al: Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. *BMJ* 2000;320:1128–1134.

TABLE 2-6. *ABPM in clinical situations*

Certain potential problems should be recognized: ABPM may cause mechanical trauma (Mansoor and White, 1994); sleep may be disturbed and raise the BP (Heude et al., 1996); reductions in usual activity will alter the readings (Costa et al., 1999).

Equipment

The noninvasive 24-hour ABPM systems now available use a standard arm cuff that is inflated at predetermined intervals, usually every 15 to 30 minutes during the day and every 30 to 60 minutes during the night, by a small pump. The individual BPs measured throughout the 24 hours are stored in the unit worn by the patient and later are read by a computer that prints all of the readings (Fig. 2-1), along with the mean plus or minus standard deviations for whatever intervals are desired.

As more of these devices are being marketed, the BHS and the AAMI have established protocols for accuracy and performance. As of mid-2000, 23 devices had been validated with these protocols (O'Brien et al., 2000).

Technique

Those who wish to perform ABPM would do well to read the consensus view on the technique published by a group of experts from the BHS (O'Brien et al., 2000).

Effects of Activity

As regards the effects of activity, patients should keep a diary of activities during the 24-hour period because of the often marked associated changes in BP (Table 2-2). A computer-assisted diary (Van Egeren and Madarasmi, 1988) or an electronic activity monitor worn on the dominant wrist (Gretler et al., 1993) may document activity more accurately.

Summarizing the Data

To summarize 24-hour data, in the past most investigators used the average value of all readings obtained throughout the 24-hour period. Recognizing that readings during sleep are normally considerably lower than daytime readings, making the 24-hour average lower than the day-time average, there is increasing use of the mean of all daytime (awake) and nighttime (sleep) readings, a procedure that seems sensible and appropriate. The average daytime value more closely approximates that found by multiple office or home readings and, by this method, the nighttime readings receive the attention they deserve. One continuing source of confusion is the timing of the awake and sleeping intervals. The logical approach is to use for the nighttime interval the actual times of retiring and rising (Gosse et al., 1996), which can be accurately ascertained by a motion detector (Eissa et al., 1999). To resolve the issue, O'Brien et al. (2000) recommend setting the daytime period at 0900 to 2100 (9 a.m. to 9 p.m.) and the nighttime at 0100 to 0600 (1 a.m. to 6 a.m.) and eliminating the readings in between. To reduce the costs and inconvenience of 24-hour monitoring, Sheps et al. (1994) found that a 6-hour daytime interval is adequate.

Because virtually all normotensive people have occasional high readings and virtually all fixed hypertensive patients have some normal readings, some clinicians advocate use of the load (i.e., the percentage of ambulatory BPs higher than 140 mm Hg systolic or 90 mm Hg diastolic) to diagnose hypertension (Zachariah and Sumner, 1993) and to ascertain the response to therapy (White, 1996).

Uses for Ambulatory Monitoring

Diagnosis

As noted earlier, the definitions of normal and high BP levels obtained by routine sphygmomanometry are arbitrary and still not universally agreed on. Because ABPM has been performed on far fewer people and because long-term follow-up is not yet available to establish the prognostic meaning of different BP levels, the definition of *normal* by ABPM remains uncertain. However, data from multiple studies have been used as the basis for the thresholds shown in Table 2-7 (Staessen et al., 1996) and now are widely accepted (O'Brien et al., 2000; Staessen et al., 2000). Pickering (1999b) notes, “It will never be possible to define a precise cut-off point that has any real meaning and, for the foreseeable future, the approach [shown in Table 2-7] which identifies a gray zone between definitely normal and definitely too high seems appropriate.”

Monitoring period	Normotension (mm Hg)	Ninety-fifth percentiles[a] (mm Hg)	Hypertension (mm Hg)
24-Hour	<130/80	135/82	≥135/85
Daytime	<135/85	139/87	≥140/90
Nighttime	<120/70	124/74	≥125/75

[a]The averaged ninety-fifth percentiles in the normotensive subjects (n = 5,348) enrolled in the Belgian and Japanese population studies, in the International Database, and in the Allied Irish Bank Study.

Data from Staessen JA, Bieniaszewski L, O'Brien ET, Fagard R. What is normal blood pressure in ambulatory monitoring? *Nephrol Dial Transplant* 1996;11:241–245.

TABLE 2-7. *Suggested operational threshold for ambulatory blood pressure monitoring*

As expected, higher readings are usual in older people. In 685 untreated men 70 years of age, the ninety-fifth percentile for daytime levels was 153/85 mm Hg and for nighttime was 132/73 mm Hg (Björklund et al., 2000).

Decision to Treat

Beyond the issue of what is a normal or high BP by ABPM is the more important issue: Should ABPM data be used to determine the need to treat individual patients? For now, the consensus seems to favor continued use of repeated office readings over ABPM levels (American College of Physicians, 1993; Joint National Committee, 1997). Nonetheless, I believe that people with high office readings who are found to be normotensive by either home readings or ABPM (i.e., those with white-coat hypertension) should not be labeled as hypertensive or treated with antihypertensive drugs unless hypertensive target organ damage is present.

For the large number of patients whose aver-age readings are in the gray zone, Pickering (1999b) advises, “The decision to treat patients with values of blood pressure within this zone can be left to the individual physician, and may be decided on factors other than blood pressure, such as the preference of the patient, and the presence of other risk factors.”

Prognosis

ABPM has been found to be superior to office readings in assessing the current status of target organ damage, in particular left ventricular hypertrophy (Tsioufis et al., 1999), and in predicting the future prognosis of any level of hypertension (Khattar et al., 1999; Mancia et al., 1997b; Ohkubo et al., 2000; Perloff et al., 1991; Verdecchia et al., 1996). A striking example of the closer relation to subsequent cardiovascular risk of ABPM levels than of conventional office readings are the data from the placebotreated half of a group of 808 older patients enrolled in the Systolic Hypertension in Europe trial (Staessen et al., 1999). As seen in Figure 2-10, the various elements of the ABPM recording were much more closely correlated to the 2-year incidence of cardiovascular events than was the office (conventional) BP.

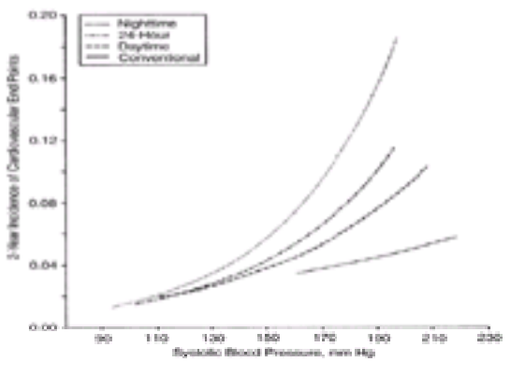

FIG. 2-10. The relation of systolic blood pressure by conventional (office) or 24-hour daytime and nighttime ambulatory measurements at entry as predictors of the 2-year incidence of cardiovascular end points in the placebotreated older patients with systolic hypertension. Incidence is given as a fraction (i.e., 0.02 is an incidence of 2 events per 100 people). Using multiple Cox regression, the event rate was standardized to female gender, mean age of 69.6 years, no previous cardiovascular complications, nonsmoking status, and residence in western Europe. (Modified from Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs. ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999;282:539–546.)

Another specific situation wherein ABPM provides better prognostic information than do office readings is the presence of hypertension during pregnancy (Bellomo et al., 1999). ABPM also was found to predict the development of preeclampsia in pregnant diabetic women (Flores et al., 1999).

Therapy

ABPM has shown that some drugs thought to have a duration of action long enough to allow for once-a-day dosing may not last long enough (Neutel et al., 1990), whereas other drugs thought to be relatively shorter-acting may be capable of sustained once-a-day effectiveness (Canter et al., 1994). ABPM can be particularly helpful in assessing an individual patient's apparent resistance to increased therapy (Pickering, 1988) (Fig. 2-11). Some patients who appear to be resistant in the office are found to be responsive when their BPs are recorded at home (Mejia et al., 1990 Redon et al., 1998; Waeber et al., 1987).

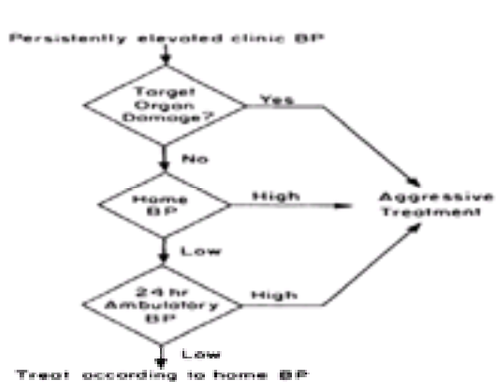

FIG. 2-11. Proposed schema of blood pressure (BP) measurement for patients with apparently resistant hypertension. [From Pickering TG. Blood pressure monitoring outside the office for the evaluation of patients with resistant hypertension. *Hypertension* 1988; 11(Suppl 2):96–100, with permission.]

ABPM has also been shown to be helpful in minimizing the amount of drug therapy needed to control hypertension, on the one hand (Staessen et al., 1997b), and in assuring that enough therapy is provided to patients whose office readings appear to be acceptable, on the other (Schillaci et al., 2000). In a parallel-group trial of 419 patients with office diastolic BP that averaged 95 mm Hg or higher, half were randomly assigned to have their therapy adjusted on the basis of ABPM, with the other half to continue office readings (Staessen et al., 1997b). At the end of an average follow-up of 6 months, more of the ABPM patients than the office-based patients

were not on drug therapy (26% versus 7%) and fewer ABPM patients had progressed to multiple drugs (27% versus 42%). Nonetheless, left ventricular mass (used as a surrogate for morbidity) and symptoms were similar in the two groups.

On the other hand, Schillaci et al. (2000) found that, among a group of 395 uncomplicated, treated hypertensive patients whose office BPs averaged 142/89 mm Hg, those whose ABPM readings were in the highest tertile had more features of left ventricular dysfunction than did those in the lower two tertiles.

New Drug Evaluation

In addition to the more accurate information ABPM provides about efficacy, there are many reasons why ABPM should be a major part of the evaluation of new drugs (Elliott, 1996; White, 2000). First, drugs may have different effects on office and ambulatory readings. In one study, the response to two b-blockers was equal according to office readings but, with ABPM, significant differences in both efficacy and duration of action were noted (Neutel et al., 1993). The tendency for office readings to decrease spontaneously as patients overcome the alerting reaction may increase the apparent efficacy of a drug (Parati et al., 1996). Second, ABPM is the only way to ascertain the efficacy of a drug during the critical early morning hours when the BP spontaneously rises. Third, by removing those who are white-coat hypertensives and therefore less responsive to any therapy, and improving the accuracy of BP measurements, ABPM may decrease the number of subjects needed to document detectable effects by a factor of four (Coats et al., 1992).

CONCLUSION

Despite all the reasons that home and ambulatory measurements are better than office readings, for now office sphygmomanometry will continue to be the primary tool for diagnosing and monitoring hypertension. Home readings should be widely used both to confirm the diagnosis and to provide better assurance of appropriate therapy. Ambulatory monitoring should be increasingly used to look for white-coat hypertension, to evaluate apparent resistance to therapy, and to determine the adequacy of therapy, particularly during sleep and the early morning hours.

We next turn to the mechanisms responsible for elevated BP in 95% of those with hypertension [i.e., those with primary (essential) hypertension].

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3
Primary Hypertension: Pathogenesis

As noted in the previous chapters, as much as 95% of all hypertension is of unknown cause. In the absence of a known cause, there is no obvious name for the disease. *Essential* may be mistakenly interpreted to infer an essential need for higher pressure to push blood through vessels narrowed by age. The term *benign* has been buried along with the millions of unfortunate victims of uncontrolled hypertension. *Idiopathic* seems a bit unwieldy; so I have chosen *primary* simply to distinguish it from all the remaining hypertensive diseases, which are “secondary” to known causes.

GENERAL CONSIDERATIONS

Use of the new tools of molecular biology promises to uncover more of the basic mechanisms of primary hypertension than has been possible with the relatively crude observational techniques of the past. In particular, the completion of the mapping of the human genome has added to the prospects of better understanding of the genetic causes of hypertension and its contribution to target organ damage as well as to the development of gene theories and more specific targeting of drugs through pharmacogenetics (Turner and Boerwinkle, 2000). As summarized by O'Shaughnessy (2001):

> A more complete understanding of the genetic basis of essential hypertension should be possible in the coming years using new strategies that take advantage of the information provided by the Human Genome Project. This knowledge will irrevocably change the way we approach this disease in terms of its diagnosis, risk assessment for end-points such as stroke and heart disease, and the customised treatment that might be offered in the future.

Nonetheless, the identification of specific genetic mechanisms will only point the way to aberrant physiologic pathways, so that the integration of observational data will still be needed. For example, the finding of a link between polymorphisms of the angiotensinogen gene and hypertension (Jeunemaitre et al., 1992, 2000) and the presence of increased levels of plasma angiotensinogen in subjects with higher parental and personal blood pressure (BP) (Watt et al., 1992) support a role for increased synthesis of angiotensinogen in hypertension but do not explain how this translates into elevated BP. We must continue to construct reasonable hypotheses from multiple, separate pieces of data, thereby developing models with broad explanatory powers.

The continued need for such integrated hypotheses is even more obvious given the multifactorial nature of hypertension. As noted by Turner and Boerwinkle (2000):

> Blood pressure levels are controlled by a complex combination of processes that influence cardiac output and peripheral vascular resistance. Many physiological, biochemical, and anatomic systems contribute to the determination of an individual's blood pressure level; therefore, multiple genes potentially influence interindividual differences in blood pressure. Because blood pressure control involves a redundancy of traits with balancing pressor and depressor roles, the impact of any one gene may be reduced as its effect is transmitted across intervening levels of biological organization. In addition, the complexity of blood pressure regulation suggests that there is a substantial genetic heterogeneity. Hence, individuals with the same blood pressure level do not necessarily have the same genotype on relevant loci, nor do individuals with the same genotype at particular loci necessarily have the same blood pressure level.

Before considering the specific genetic and environmental factors that may be responsible for hypertension, a few generalizations are in order:

- The relevance of data from animal models is highly questionable. Even though 70% of cur-rent research on hypertension is being done on rats or other small animals (Kwitek-Black and Jacob, 2001; Sugiyama et al., 2001), the relevance of such data to the human condition is suspect. For example, transgenic hypertensive rats develop fulminant hypertension at an early age despite low levels of renin in the plasma and kidney (Lee et al., 1996), quite unlike what is seen in humans. Therefore, this discussion will almost exclusively examine data from human studies.
- Few analytic techniques are available to measure accurately and repetitively small changes in various hemodynamic functions involved in the development of hypertension that may occur over many years. Cross-sectional observations may never be able to uncover the sequential changes that could be revealed by longitudinal studies.
- Even when studies are performed among adolescent and borderline hypertensives, the beginnings of the disease may have already been missed. In the absence of a marker to identify the prehypertensive individual, before the BP has risen, we may be viewing the process after the initiating factors are no longer recognizable, obscured by adaptations invoked by the rising pressure. An editorial some time ago in the *Lancet* (Anonymous, 1977) describes the situation aptly:

  > Blood pressure is a measurable end product of an exceedingly complex series of factors including those which control blood vessel calibre and responsiveness, those which control fluid volume within and outside the vascular bed, and those which control cardiac output. None of these factors is independent: They interact with each other and respond to changes in blood pressure. It is not easy, there-fore, to dissect out cause and effect. Few factors which play a role in cardiovascular control are completely normal in hypertension: Indeed, normality would require explanation since it would suggest a lack of responsiveness to increased pressure.

- Although the concept of a single underlying abnormality that begins the hemodynamic cascade toward sustained hypertension is attractive, there may be no such single defect. In view of the multiple factors involved in the control of the BP, the concept of a multifaceted mosaic, introduced by Page (1963), may be more appropriate, as unattractive as it may be to those who prefer to believe that for every biologic defect there should be a single, specific cause.
- The search may be misdirected: In looking for the mechanisms of primary hypertension, we may need to separate the disorder into many distinct syndromes, each with its own mechanisms. An analogy to fever seems appropriate (Brown, 1996). Like BP, body temperature is normally distributed, but when it rises beyond a certain level (37°C in place of 140/90 mm Hg), an abnormality is usually responsible. When fever is present, specific causes are sought and increasingly can be recognized, although some remain “fever of unknown origin.” So it is with hypertension: During the last 50 years, multiple specific identifiable causes have been recognized although, as is described in Chapter 9, Chapter 10, Chapter 11, Chapter 12, Chapter 13, Chapter 14 and Chapter 15 they comprise only a small percent-age of all hypertensives. There may be more such identifiable types still unrecognized.

As we shall see, more and more differences are being identified within the population of patients with primary hypertension. For now, however, unifying hypotheses seem appropriate, with the recognition that there may be consider-able variations in the role of various components at different times and stages and in different people. Before examining the specific hypotheses that may explain the development of hypertension, the role of genetics will be considered.

ROLE OF GENETICS

Hypertension clusters in families, some investigators finding a stronger contribution from the father (Rebbeck et al., 1996), others from the mother (Fuentes et al., 2000). Of greater relevance is the importance of a family history in early coronary disease or stroke; those 10% to 15% of families with such a positive history, who are responsible for 70% to 90% of cardiovascular disease, can thereby be earmarked for further study and, hopefully, preventive measures (Williams et al., 2001).

Estimates of the genetic contribution to the variability of BP range from 30% to 50% (Dominiczak et al., 2000). The relative risk that a sibling of a hypertensive person will be hypertensive as compared to the risk in the general population is approximately 3.5 (O'Shaughnessy, 2001). This is obviously much less than the 500-fold greater risk seen with a single gene disorder such as cysticfibrosis but is in keeping with the range of other polygenic disorders such as type 1 diabetes (relative risk,

~15) or coronary heart disease (relative risk, ~2).

The fundamental problem in ascertaining the genetic contribution was described by Swales (1994):

> Blood pressure is the final phenotype resulting from the complex impact of environmental influences on the expression of a number of genes. Gene expression, of course, occurs at a subcellular level, and is progressively modified by other genetically and environmentally conditioned influences at cellular, tissue, organ and finally whole-body level. This will substantially dilute single-gene effects on blood pressure. Analysing changes which occur at cell, tissue or organ level, and which are causally related to blood pressure on one hand and more closely to gene expression on the other, may help us to identify the mechanism of high blood pressure. Such intermediate phenotypes . . . range from processes in which the environmental component may be fairly small (such as changes in electrolyte transport by the individual smooth muscle cell) to phenotypes much closer to blood pressure regulation such as sympathetic nervous system reactivity.

Known Genetic Defects

Monogenic Syndromes

Long before the completion of the mapping of the human genome, a tremendous amount of research has attempted to unravel the genetics of hypertension. As a consequence, a small number of rare monogenic forms of hypertension have been identified (Lee et al., 2000), and a large number of associations have been recognized (Gambaro et al., 2000). As is described in more detail in Chapter 13 and Chapter 14, virtually all the monogenic syndromes discovered thus far have involved increased renal sodium reabsorption arising through either primary defects in trans-port systems (Meneton and Warnock, 2001) or stimulation of mineralocorticoid receptor activity (Geller et al., 2000; Lifton, 1996) (Fig. 3-1). Currently, the only exception is the rare familial syndrome with autosomal dominant brachydactyly and short stature that has been mapped to chromosome 12p (Toka et al., 1998) and that may involve a neurovascular defect.

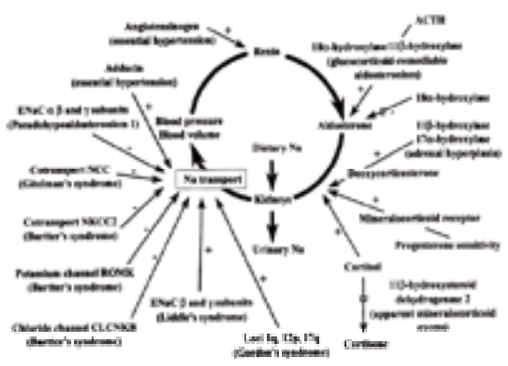

FIG. 3-1. Mutations and polymorphisms altering blood pressure in humans. All the genes are involved directly or indirectly in the control of renal sodium (Na) reabsorption. The mutations have been found in monogenic forms of hypertension or hypotension, except the polymorphisms in the angiotensinogen and adducin genes, which have been linked to essential human hypertension. The signs + or – refer to a mechanism leading to hypertension or hypotension, respectively. The *double lines* across the *arrows* indicate an impaired synthesis pathway. ACTH, adrenocorticotropic hormone; ENaC, epithelial sodium channel. [Reprinted from Meneton P, Warnock DG. Involvement of renal apical Na transport systems in the control of blood pressure. *Am J Kidney Dis* 2001;37(Suppl 2):S39–S47, with permission.]

Candidate Genes

The number of reported associations between genetic polymorphisms and hypertension continues to expand (Table 3-1). Most of the claims have been found to apply to only limited numbers of patients, so that no single candidate gene has yet been shown to contribute to BP variation in general. All that is certain now is that multiple genes are involved and that interactions between multiple loci rather than variants of a single gene underlie the genetic basis of hypertension (Williams SM et al., 2000).

Adenosine type A_{2a} receptor
α-Adducin
β_2-Adrenergic receptor
Angiotensin type 1 receptor
Angiotensinogen
Atrial natriuretic peptide and receptor
Bradykinin type 2 receptor
Dopamine D1 receptor
Endothelial nitric oxide synthase
Endothelin-1 and -2
Epithelial sodium channel, β-subunit
G-protein, β_3-subunit
11β-Hydroxysteroid dehydrogenase type 2
Insulinlike growth factor-1
Insulin receptor substrate 1
Neutral endopeptidase
Prostacyclin synthase
Prostaglandin EP_2 receptor
Renin
Sodium amiloride–sensitive channel
Sodium-chlorothiazide–sensitive cotransporter
Sodium-potassium-chloride cotransporter
Sodium–proton exchanger 3
Transforming growth factor-β_1

TABLE 3-1. *Some of the candidate genes for which polymorphisms have been reported in human hypertension*

Rather than attempt to describe the ever-changing literature, a few general points deserve emphasis:

- Genome-wide linkage analyses show that hypertension is polygenic (Krushkal et al., 1999; Perola et al., 2000; Sharma et al., 2000). Multiple chromosomes are involved, including chromosome 17 (Levy et al., 2000) and the Y chromosome (Ellis et al., 2000).
- Insertion/deletion polymorphisms of the angiotensin-converting enzyme (ACE) are related to the progression of renal damage and the responses to renoprotective therapy (Redon et al., 2000) and to exercise (Montgomery et al., 1999).
- Polymorphisms of multiple genes involving the renin-angiotensin system (RAS) may be involved in sodium sensitivity and the response to inhibitors of the system. These include the angiotensinogen gene (Hunt et al., 1998), the ACE gene (Giner et al., 2000), and the angiotensin II (AII) type 1 receptor gene (Miller et al., 1999).
- Mutations in two of the genes known to be responsible for monogenic forms of lowrenin hypertension—the aldosterone synthase (Tamaki et al., 1999) and the 11 b-hydroxysteroid dehydrogenase-2 (Agarwal et al., 2000) genes—have also been identified in less affected low-renin hypertensives. Mutations of the epithelial sodium channel, recognized to be the cause of increased renal sodium reabsorption in Liddle's syndrome, have been found to be frequent among low-renin blacks in London (Baker et al., 1998) but not in Paris (Persu et al., 1999). Disparities such as this are common in the literature.
- The inconsistencies and limitations of single-locus candidate gene association and linkage studies have pointed to the need for more systematic studies of multiple genes and environmental factors (Kardia, 2000). An example is the path analysis of insulin sensitivity and BP in Hispanic families with a hypertensive proband, which provided estimates of the genetic factors both associated with and independent of body weight (Xiang et al., 2001).

Limitations of Genetics

Even as the scope of genetic research is broadened, cautions about the limitations of what can be expected in the future are bringing the initial overenthusiasm about the “genetic revolution” into a more guarded perspective (Corvol et al., 1999). In addition to the fundamental problems of the complexity of BP regulation, Weatherall (1999) notes that “the complexity of the genotype-phenotype relationship has undoubtedly been underestimated. . . . It is far from certain that we will ever reach a stage in which we can accurately predict the occurrence of some of the common disorders of Western society at any particular stage in an individual's life.” As

Holtzman and Marteau (2000) warn:

> It would be revolutionary if we could deter-mine the genotypes of the majority of people who will get common diseases. The complexity of the genetics of common diseases casts doubt on whether accurate prediction will ever be possible. Alleles at any different gene loci will increase the risk of certain diseases only when they are inherited with alleles at other loci, and only in the presence of specific environmental or behavioral factors. Moreover, many combinations of predisposing alleles, environmental factors, and behavior could all lead to the same pathogenic effect.

Genes versus Environment

As the complexities of the genotype-phenotype relationships are being addressed, a simple portrayal of the underlying interactions should be useful. As described by Carretero and Oparil (2000):

> Theoretically, in a population unaffected by hypertensinogenic factors, BP will have a normal distribution; it will be skewed to the right and will have a narrow base or less variance [Fig. 3-2, *continuous line*]. When 1 hypertensinogenic factor is added to this population, such as increased body mass, one would expect the normal distribution curve to be further skewed to the right; consequently the base will be wider (more variance) and the curve will be flatter [Fig. 3-2, *broken line*]. If a second hypertensinogenic factor such as alcohol intake is added to increased body mass, the curve will be skewed more to the right and the variance will increase further, with more subjects classified as hypertensive [Fig. 3-2, *dotted line*].

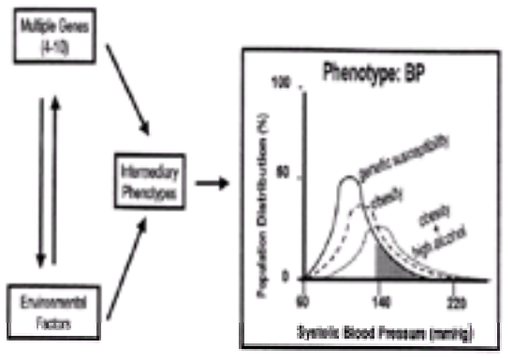

FIG. 3-2. Interaction among genetic and environmental factors in the development of hypertension. The left side of the figure shows how environmental factors and multiple genes responsible for high blood pressure (BP) interact and affect intermediary phenotypes. The result of these intermediary phenotypes is BP with a normal distribution skewed to the right. Continuous line indicates the theoretic BP of the population that is not affected by hypertensinogenic factors; shaded area indicates systolic BP in the hypertensive range. Broken lines and dotted lines indicate populations in which one (obesity) or two (obesity plus high alcohol intake) hypertensinogenic factors have been added. (Reprinted from Carretero OA, Oparil S. Essential hypertension. *Circulation* 2000;101:329–335, with permission.)

> Discovering which genetic variations place BP on the left or right side of the distribution curve is of both theoretical and practical importance because it could help the physician to better treat or cure hypertension. Recognition of the hypertensinogenic factors may allow nonpharmacological prevention, treatment, or cure of hypertension.

As will be noted in greater detail, the boundaries between genes and environment have been blurred further by the recognition of intrauterine growth retardation as an apparently strong predictor of subsequent hypertension. Obviously, it would be easy to mistake prenatal influences for genetic defects.

Genes versus Race

The mechanisms and consequences of hypertension differ between different racial and ethnic groups. Although attempts have been made to identify specific genes that may be responsible for racial differences (Kotchen et al., 2000; Larson et al., 2000), Cooper and Zhu (2001) conclude, “On a molecular basis, we may never be able to dissect our species into subgroups.” Goodman (2000) goes further: “Race does not account for human genetic variation, which is continuous, completely structured, constantly changing, and predominantly within 'races'.”

Promise of Genetics

Although a complete unraveling of the genotype-phenotype relationships involved in human hypertension may never be achieved, a great deal of good may come along the way. We can hope for another discovery such as the low-density lipoprotein receptor mutations underlying familial hypercholesterolemia that led to the development of the remarkably effective statin drugs. Lacking that impact, it may still be possible to use gene therapy, as is being applied to animal models through overexpression of vasodilator genes or antisense knockdown of vasoconstrictor genes (Gelband et al., 2000). Perhaps closer to practical application is the use of pharmacogenetics, the identification of genetic factors that contribute to interpatient and interdrug variations in response to specific anti-hypertensive drug therapies (Turner et al., 2001). As noted earlier, polymorphisms of genes controlling the RAS have been found to be associated with varying responses of drugs that work on that system. As Turner et al. (2001) enthusiastically conclude:

> Knowledge of genes that contribute to the disease process and genes that influence drug responses will facilitate the development of new drugs and therapeutic approaches that are based on a deeper understanding of the molecular determinants of the disease and the response to therapy. Drugs that are more specific for the molecular characteristics of individual patients should contribute to greater efficacy and reduced toxicity. Certainly, the collection and analyses of unprecedented amounts of genetic information in the coming years has the potential to revolutionize the way drugs are developed and the approaches taken to diagnose, treat and pre-vent hypertension and its associated target organ diseases.

We will now examine various environmental factors that likely interact with multiple genes, including stress, obesity, and electrolyte intake. These factors will be considered as part of a construct that covers multiple possible pathways to hypertension.

OVERVIEW OF PATHOGENESIS

The pressure required to move blood through the circulatory bed is provided by the pumping action of the heart [cardiac output (CO)] and the tone of the arteries [peripheral resistance (PR)]. Each of these primary determinants of the BP is, in turn, determined by the interaction of the “exceedingly complex series of factors” (Anonymous, 1977) displayed in part in Figure 3-3.

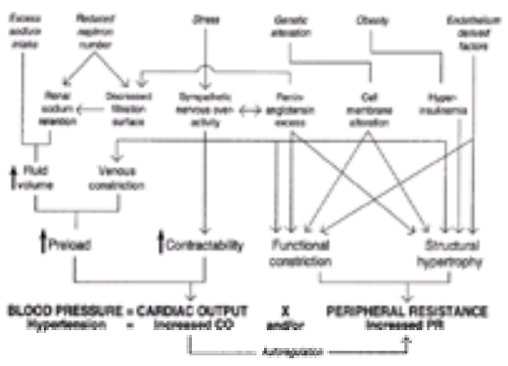

FIG. 3-3. Some of the factors involved in the control of blood pressure that affect the basic equation:blood pressure = cardiac output × peripheral resistance.

Hypertension has been attributed to abnormalities in virtually every one of these factors. Each will be examined and attempts will be made along the way to integrate

them into logical hypotheses. It is unlikely that all these factors are operative in any given patient; but multiple hypotheses may prove to be correct, because the hemodynamic hallmark of primary hypertension—a persistently elevated vascular resistance—may be reached through a number of different paths. Before the final destination, these may converge into either structural thickening of the vessel walls or functional vasoconstriction. Moreover, individual factors often interact, and the interactions are proving to be increasingly complex. For instance, the presence of a hyperdynamic circulation in parents was closely correlated to the presence of overweight, upper body fat predominance, hyperinsulinemia, and increased BP in their children (Palatini et al., 1999).

We will follow the outline shown in Figure 3-3, recognizing that the position of each factor in the outline is not necessarily in the order that the hemodynamic cascade follows in the pathogenesis of hypertension. Without knowing what starts the process, we can lay out only a preliminary blueprint that can be used by beginning at multiple sites.

CARDIAC OUTPUT

An increased CO has been found in some young, borderline hypertensives who may display a hyperkinetic circulation. If it is responsible for the hypertension, the increase in CO could logically arise in two ways: either from an increase in fluid volume (preload) or from an increase in contractility from neural stimulation of the heart (Fig. 3-3). However, even if it is involved in the initiation of hypertension, the increased CO likely does not persist, because the typical hemodynamic finding in established hypertension is an elevated PR and normal CO (Cowley, 1992).

Heart Rate

Although an increased heart rate may not simply be a reflection of a hyperdynamic circulation or an indicator of increased sympathetic activity (Grassi et al., 1998), multiple epidemiologic surveys have shown that an elevated heart rate is an independent predictor of the development of hypertension (Palatini and Julius, 1999). Moreover, both an elevated heart rate and decreased heart rate variability are predictors of cardiovascular mortality (Kikuya et al., 2000), at least in part because they are associated with other cardiovascular risk factors (Morcet et al., 1999). Heredity contributes approximately 20% of the variance in both heart rate and its variability (Singh et al., 1999).

Hyperkinetic Hypertensives

Numerous investigators have described hypertensives, mostly young, who definitely have high CO (Finkielman et al., 1965; Jiang et al., 1995). Using noninvasive echocardiography to study young borderline hypertensives (average age, 33 years), 37 of 99 subjects were found to have increased heart rate, cardiac index, and forearm blood flow caused by an excessive autonomic drive (Julius et al., 1991c).

Most of these features could reflect anxiety over both the knowledge that they were hypertensive (Rostrup et al., 1991) and the procedures used in the studies (Palatini et al., 1996). Moreover, these features have not been observed either in small groups of normotensive children who are likely to develop hypertension because both their parents were hypertensive (van Hooft et al., 1993) or in almost 500 participants in the Framingham Heart Study who developed hypertension (Post et al., 1994). In this echocardiographic follow-up in Framingham, initially increased heart rate and cardiac index were related to the subsequent onset of hypertension, but none of the hemodynamic evidences of a hyperkinetic circulation was a significant predictor of the development of hypertension after controlling for age and baseline BP.

Cardiac Hypertrophy

Nonetheless, significant increases in left ventricular mass have been recognized in the stillnormotensive children of hypertensive parents (Koren and Devereux, 1993; van Hooft et al., 1993). Such left ventricular hypertrophy (described in greater detail in Chapter 4) has generally been considered a compensatory mechanism to an increased vascular resistance (afterload). However, it could also reflect a primary response to repeated neural stimulation and, thereby, could be an initiating mechanism for hypertension (Julius et al., 1991c) as well as an amplifier of CO that reinforces the elevation of BP from arterial stiffening (Segers et al., 2000).

Increased Fluid Volume

A second mechanism that could induce hypertension by increasing CO would be an increased circulating fluid volume (preload). However, in most studies, subjects with high BP have a lower blood volume and total exchangeable sodium than do normal subjects (Harrap et al., 2000).

Relation of Blood Volume to Blood Pressure

When the BP was compared to the total blood volume in 48 healthy subjects and 106 patients with fairly early and mild primary hypertension, an interesting relationship was observed (Lon-don et al., 1977) (Fig. 3-4). A negative correlation was found in the healthy subjects but not in the hypertensives, with 80% of the hypertensives being outside the 95% confidence limits of the normal curve. The authors interpret their data as indicating a quantitative disturbance in the pressure-volume relationship in primary hypertension (i.e., a plasma volume that is inappropriately high for the level of BP). Thus, even if absolute values are reduced, a relatively expanded blood volume may be involved in the maintenance of hypertension.

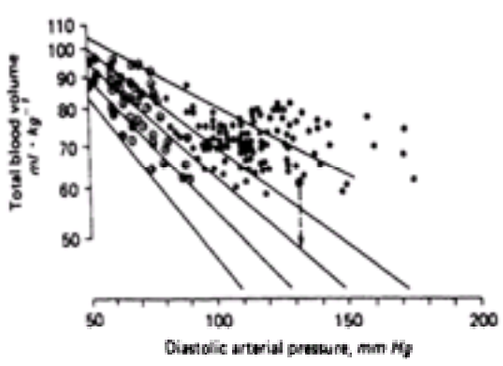

FIG. 3-4. Relation between diastolic blood pressure and total blood volume in 48 normotensive (*open circles*) and 106 hypertensive (*solid circles*) subjects. Only 20% of the hypertensive patients fell within the 95% confidence limits of the normal curve. The total blood volume definition (*solid circles with arrow*) represents the degree of the pressure-volume disturbance. (Reprinted from London GM, Safer ME, Weiss YA, et al.Volume-dependent parameters in essential hyper-tension. *Kidney Int* 1997;11:204– 208, with permission.)

Redistribution of Blood Volume

Even without an expanded total volume, blood may be redistributed so that more is in the central or cardiopulmonary component because of greater peripheral vasoconstriction (Schobel et al., 1993). Venous return to the heart would thereby be increased and could mediate an increased CO. However, serious reservations have been expressed about both the methods used to measure cardiopulmonary blood volume and the theoretic concept that if it were increased, it would persist rather than be quickly normalized so that CO would be increased only transiently (Birkenhäger and de Leeuw, 1984).

This brings us to the final feature about CO. Even if it is involved in the initiation of hyper-tension, once hypertension is established, CO usually is not increased, but PR is elevated.

Autoregulation

Definition and Description

The pattern of initially high CO giving way to a persistently elevated PR has been observed in a few people and many animals with experimental hypertension. When animals with markedly reduced renal tissue are given volume loads, the BP rises initially as a consequence of the high CO but, within a few days, PR rises and CO returns to near the basal level (Guyton, 1992) (Fig. 3-5). This changeover has been interpreted as reflecting an intrinsic property of the vascular bed to regulate the flow of blood, depending on the metabolic need of tissues. This process, called *autoregulation*, was described by Borst and Borst-de Geus (1963) and demonstrated experimentally by Guyton and Coleman (1969). With increased CO, more blood flows through the tissues than is required, and the increased flow delivers extra nutrients or removes additional metabolic products; in response, the vessels constrict, decreasing blood flow and returning the balance of supply and demand to normal. Thus, PR increases and remains high by the rapid induction of structural thickening of the resistance vessels, as described in the section Peripheral Resistance.

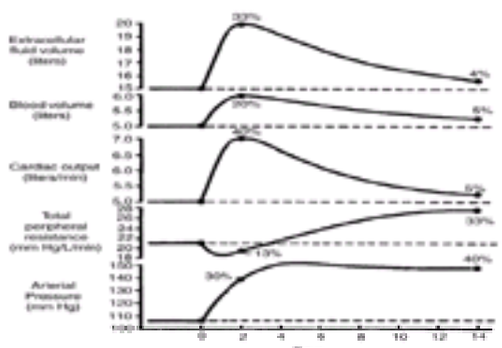

FIG. 3-5. Progressive changes in important circulatory system variables during the first weeks in volume-loading hypertension. The initial rise in cardiac output is the basic cause of the hypertension. Subsequently, the autoregulation mechanism returns the cardiac output to almost normal and at the same time causes a secondary increase in total peripheral resistance. [Reprinted from Guyton AC. Kidneys and flu-ids in pressure regulation. *Hyper-tension* 1992;19(Suppl 1):12–18, with permission.]

Similar conversion from an initially high CO to a later increased PR has been shown in hypertensive people (Andersson et al., 1989; Julius, 1988b; Lund-Johansen, 1989). In Lund-Johansen's (1989) study, younger (17-to 29-year-old) and older (30- to 39-year-old) mild hypertensives were restudied both at rest and during exercise after 10 and then 20 years without intervening therapy. As the over-all BPs rose, the CO fell and PR increased (Fig. 3-6).

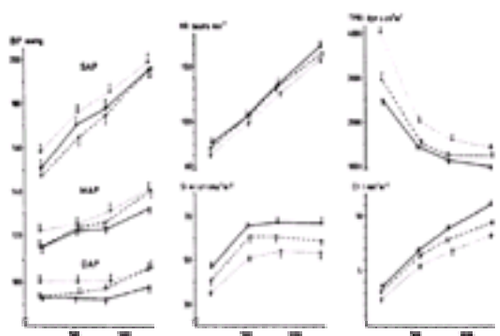

FIG. 3-6. Central hemodynamics at rest and during exercise in 17- to 29-year-olds at the first study (*solid circles, solid line*) and at restudy after 10 years (*open triangles, dashed line*) and 20 years (*open circles, dotted line*). Mean values are reported. Note the marked increase in the total peripheral resistance index (TPRI) from study 1 to study 3 and the reduction in stroke index (SI) and cardiac index (CI) from study 1 to study 3. BP, blood pressure; DAP, diastolic arterial blood pressure; HR, heart rate; MAP, mean arterial blood pressure; SAP, systolic arterial blood pressure; Vo2, oxygen consumption. [Reprinted from Lund-Johansen P. Central haemodynamics in essential hypertension at rest and during exercise. *J Hypertens* 1989;7(Suppl 6):S52–S55, with permission.]

Problems with the Autoregulation Model

The role of autoregulation in the conversion of a high CO to a high PR has been questioned for various reasons. These include the finding that patients with increased CO also have increased oxygen consumption, rather than the lower level that should be seen if there were overperfusion of tissues, as entailed in the autoregulation concept (Julius, 1988b).

Julius (1988b) considers autoregulation to be an unlikely explanation for the switch from high CO to increased PR and offers another: structural changes that decrease the cardiac responses to nervous and hormonal stimuli but enhance the vascular responses. His proposal states that the “hemodynamic transition can be explained by a secondary response to elevated blood pressure. The heart becomes less responsive as a result of altered receptor responsiveness and decreased cardiac compliance, whereas the responsiveness of arterioles increases because of vascular hyper-trophy, which leads to changes in the wall-to-lumen ratio” (Julius, 1988b).

Nonetheless, the autoregulatory model does explain the course of hypertension in volume-expanded animals and people, particularly in the presence of reduced renal mass (Fig. 3-5). Ledingham (1989) defends autoregulation as the “dominant factor” leading to the rise in PR in hypertension. Moreover, there is additional evidence in favor of volume expansion in the pathogenesis of the disease, reflecting the effect of too much sodium coming in and not enough going out, the latter because of a less-than-normal number of nephrons.

EXCESS SODIUM INTAKE

Figure 3-3 shows excess sodium intake inducing hypertension by increasing fluid volume and preload, thereby increasing CO. As will become obvious, sodium excess may increase BP in multiple other ways also.

Overview

After reviewing the available evidence relating sodium intake to hypertension, most investigators determine that “there is conclusive evidence that dietary salt is positively associated with BP and that BP can be lowered with reductions in sodium intake of 40 to 50 mmol [per day] in both hypertensive and nonhypertensive persons” (Chobanian and Hill, 2000). Some authors, reviewing the same evidence, do not agree (Brown et al., 1984), whereas others accept a role for sodium but question the wisdom of advocating sodium restriction in view of potential hazards (Alderman, 2000).

The basis for the generally accepted necessary but not, in itself, sufficient role of sodium excess was stated by Denton (1997):

> Human prehistory as hunter-gatherers with inland savannah existence involved a paucity of salt. The hedonistic liking for it, physiologically apt in those circumstances, is maladaptive in Western metropolitan existence with processed food and cheap abundant salt sources. Above a threshold of 70–100 mmol Na per day, sodium intake may be directly causal of BP

increase in sensitive individuals, and permissive of action of other factors such as low K and Ca intake, stress, obesity and alcohol to influence BP.

As will be noted, diets in industrialized societies contain many times the daily adult sodium requirement, an amount that is beyond the threshold level needed to induce hypertension (Fig. 3-7). Only part of the population may be susceptible to the deleterious effects of this high sodium intake, presumably because these individuals have an additional renal defect in sodium excretion. As portrayed in Figure 3-7, because almost everyone in industrialized societies ingests an excess of sodium beyond the threshold needed to induce hypertension, it may not be possible to show a relationship between sodium intake and BP in these populations. The absence of such a relationship in no way detracts from the possible role of excess dietary sodium in causing hypertension.

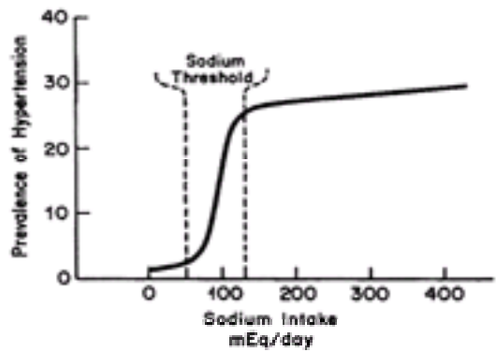

FIG. 3-7. Probable association between usual dietary sodium intake and the prevalence of hyper-tension in large populations. (Reprinted from Kaplan NM. Dietary salt intake and blood pressure. *JAMA* 1984;251:1429–1430, Copyright 1984, American Medical Association, with permission.)

Dietary Sodium-Potassium Ratio

This section focuses on sodium excess, but both experimental data (Tobian, 1991) and epidemiologic evidence (Stamler et al., 1997) support a close association between hypertension and a high sodium-potassium ratio in humans. A low potassium intake may be as responsible as a high sodium intake (Geleijnse et al., 1996) but, as the following discussion points out, most evidence favors a primary role for sodium excess.

Dietary Chloride

Chloride, and not just sodium, may be involved in causing hypertension. In two classic rat models of sodium-dependent hypertension, hyper-tension could be induced with sodium chloride but not with sodium bicarbonate or ascorbate (Kurtz and Morris, 1983; Whitescarver et al., 1984). In people, too, the BP rises more with NaCl than with nonchloride salts of sodium (Schorr et al., 1996). This issue is largely academic, as chloride is the major anion accompanying sodium in the diet and in body fluids.

Epidemiologic Evidence

The epidemiologic evidence incriminating an excess of sodium includes the following points:

- Primitive people from widely different parts of the world who do not eat sodium have no hypertension, and their BP does not rise with age, as it does in all industrialized populations (Denton, 1997; Page et al., 1981). For example, the Yanomamo Indians of northern Brazil, who excrete only approximately 1 mmol of sodium per day, have an average BP of 107/67 mm Hg among men and 98/62 mm Hg among women aged 40 to 49 (Oliver et al., 1975).
- The lack of hypertension may be attributable to other differences in lifestyle, but comparisons made in groups living under similar conditions relate the BP most directly to the level of dietary sodium intake (Lowenstein, 1961; Page et al., 1981). Moreover, when primitive peoples who are free of hypertension adopt modern lifestyles, including increased intake of sodium, their BP rises and hypertension appears (Klag et al., 1995; Poulter et al., 1990).
- Significant correlations between the level of salt intake and the levels of BP and frequency of hypertension have been found in most large populations (Beard et al., 1997; Elliott, 1991; Law et al., 1991; Stamler et al., 1996) but not in all (Smith et al., 1988). The strongest data come from the Intersalt study, which measured 24-hour urine electrolytes and BP in 10,079 men and women aged 20 to 59 years in 52 places around the world (Elliott et al., 1996; Intersalt Cooperative Research Group, 1988). For all 52 centers, there was a positive correlation between sodium excretion and both systolic BP and diastolic BP but an even more significant association between sodium excretion and the changes in BP with age (Fig. 3-8). Few populations were found whose levels of sodium intake were in the 50- to 100-mmol per day range, wherein the threshold for the sodium effect on BP likely resides. However, the virtual absence of either hypertension or a progressive rise in BP with advancing age in populations with an average sodium ingestion of only about 50 mmol per day supports the concept of a threshold (Fig. 3-7).

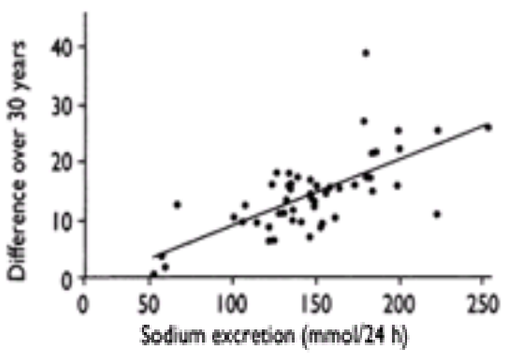

FIG. 3-8. Plot of the difference in systolic blood pressure over 30 years (age 55 minus age 25) in relation to median urinary sodium excretion across 52 populations. (Reprinted from Stamler J, Elliott P, Dyer AR, et al. Commentary: sodium and blood pressure in the Intersalt study and other studies. *BMJ* 1996;312:1285–1287, with permission.)

As noted by Denton (1997), our current high sodium–low potassium intake is a recent phenomenon in the span of human existence, beginning only a few hundred years ago and accelerated by modern food processing, which adds sodium and removes potassium. Table 3-2 shows that our herbivorous ancestors probably consumed less than 10 mmol of sodium per day, whereas our carnivorous ancestors might have eaten 30 mmol per day (Eaton et al., 1996). Human physiology evolved in a lowsodium–high-potassium environment, and we seem ill equipped to handle the current expo-sure to high sodium and low potassium.

Nutrient	Late Paleolithic diet (assuming 35% meat)	Current American diet
Total dietary energy (%)		
Protein	30	12
Carbohydrate	45–50	46
Fat	20–25	42
Polyunsaturated-saturated fat ratio	1.41	0.44
Fiber (g per day)	86	10–20
Sodium (mg)	654	3,400
Potassium (mg)	6,370	2,400
Potassium-sodium ratio	12:1	0.7:1.0
Calcium (mg)	1,520	740

Data from Eaton SB, Eaton SB II, Konner MJ, Shostak M. An evolutionary perspective enhances understanding of human nutritional requirements. J Nutr 1996;126:1732–1740.

TABLE 3-2. *Estimated diet of late Paleolithic humans versus that of contemporary Americans*

Our current preference for a high sodium intake likely is an acquired taste, one that may develop early in childhood (Beauchamp and Engelman, 1991). In the typical diet of industrialized societies, as little as 15% of total sodium consumption is discretionary, and even less is inherent to the food, with more than 75% being added in the processing (Mattes and Donnelly, 1991). This increase in sodium intake from processed foods has been so recent that genetic adaptation has not been possible. Because evolutionary changes to preserve darwinian fitness are not needed if new environmental factors produce disability or death only after the reproductive years, modern humans may simply not be able to adapt successfully to their high sodium expo-sure (Trowell, 1980).

Experimental Evidence

The experimental evidence for a role of sodium excess in hypertension development includes the following:

- When hypertensives are sodium-restricted, their BP falls. As described more fully in Chapter 6, dramatic falls in BP may follow rigid sodium restriction (Kempner, 1948), whereas less rigid restriction to a level of 75 to 100 mEq per day has been found to lower BP modestly in most studies (Cutler et al., 1991, 1997).
- Although short periods of increased NaCl intake have been shown to raise BP in some normotensive subjects (Luft et al., 1979; Mascioli et al., 1991) but not in others (Heer et al., 2000), it may never be possible to show conclusively that salt intake causes hypertension in people, whereas it is fairly easy to do so in genetically predisposed animals (Dahl, 1972; Tobian, 1997). As seen in Figure 3-9, the most impressive evidence comes from the study on free-living chimpanzees, half of whom were given progressively increasing amounts of sodium in their food, while the other half remained on their usual low-sodium diet (Denton et al., 1995). During the 89 weeks in which the chimps received extra sodium, the BP rose an average of 33/10 mm Hg, returning to baseline after 20 weeks without added sodium. In keeping with varying sodium sensitivity, the BP rose in only seven of ten chimpanzees on the added sodium.

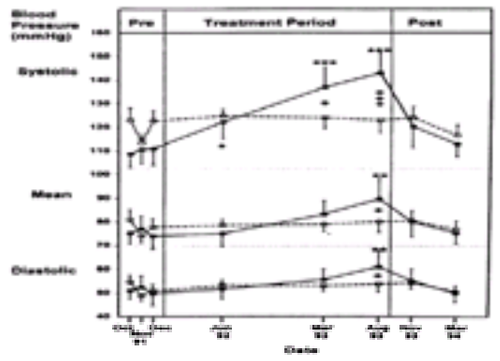

FIG. 3-9. A group of 22 chimpanzees maintained in small, long-term, stable social groups and fed a vegetable-fruit diet with the addition of infant formula were studied. The 12 control animals (*open circles*, *dotted line*) experienced no change in conditions over 2.4 years and no significant change of systolic, diastolic, or mean blood pressure (mean ± standard error of the mean). For the ten experimental animals (*solid circles*, *solid line*), 5 g per day NaCl was added to the infant formula for 19 weeks, 10 g per day for 3 weeks, and 15 g per day for 67 weeks. A 20-week period without salt addition followed. Significance values of the increase in blood pressure relative to the mean of the three baseline determinations were as follows: * p <.05, ** p <.0021; significance values of the difference between the experimental and control groups: * p <.05, *** p <.001. (Reprinted from Denton D, Weisinger R, Mundy NI, et al. The effect of increased salt intake on blood pressure of chimpanzees. *Nat Med* 1995;1:1009–1016, with permission.)

- Although long-term intervention studies that start with infants and children to confirm that sodium restriction can prevent hypertension in humans or that sodium excess can cause it are not feasible, a short-term 6-month study involving almost 500 newborn infants showed that the half whose sodium intake was reduced by nearly 50% had a 2.1–mm Hg lower systolic BP at the end of the 6 months than did the half who were on normal sodium intake (Hofman et al., 1983). Among the 35% of the participants who could be located 15 years later, those originally on the low-sodium diet had 3.6/2.2–mm Hg lower BP (Geleijnse et al., 1997). Moreover, in randomized controlled studies of hundreds of patients with high-normal BP, those patients who moderately restricted their sodium intake for 30 months or longer had lower BP and a decreased incidence of hypertension than did the patients who did not reduce their sodium intake(Stamler et al., 1989; Trials of Hypertension Prevention, 1997 ; Whelton et al., 1998).
- A high sodium intake may activate a number of pressor mechanisms (Haddy and Pamnani, 1995). These include increases in intracellular calcium (Resnick et al., 1994), insulin resistance (Suzuki et al., 2000), a paradoxical rise in atrial natriuretic peptide (Campese et al., 1996), and an upregulation of angiotensin type 1 receptors (Nickenig et al., 1998). In animals, high sodium intake induces myocardial and renal fibrosis, possibly via transforming growth factor–b_1 overexpression (Yu et al., 1998).

Parenthetically, additional damages may be associated with high sodium intake that are not mediated by the effects of sodium on BP (Aviv, 2001; MacGregor, 1997). Both in animals (Tobian and Hanlon, 1990) and in humans (Sasaki et al., 1995), a high intake of sodium increases the risk of stroke, independent of the effect on BP. Other adverse effects of high sodium intake include left ventricular hypertrophy and more rapid deterioration of renal function through hyperfiltration (MacGregor, 1997). Both osteoporosis and renal stones accompany the increase in calcium excretion that occurs with increased sodium excretion (Stamler and Cirillo, 1997). As if these damages were not enough, dietary sodium intake also is strongly correlated with stomach cancer mortality (Joossens et al., 1996) and the incidence of cataracts (Cummings et al., 2000).

Interventional Evidence

More than 100 trials exploring the effect of dietary sodium reduction on BP have been published, which demonstrate an average reduction of 5/2 mm Hg in hypertensives who lower their sodium intake to approximately 100 mmol per day (Cutler et al., 1997). More about this evidence is provided in Chapter 6.

Sensitivity to Sodium

Because almost everyone in industrialized societies ingests a high-sodium diet, the fact that only about half will develop hypertension suggests a variable degree of BP sensitivity to sodium, although obviously both heredity and interactions with other environmental exposures may be involved (Weinberger, 1996). Since Luft et al. (1977) and Kawasaki et al. (1978) described varying responses of BP to short periods of low and high sodium intake, numerous protocols have been used to determine so-called sodium sensitivity (Gerdts et al., 1999). Weinberger et al. (1986) defined sodium sensitivity as a 10–mm Hg or greater decrease in mean BP from the level measured after a 4-hour infusion of 2 L normal saline as compared to the level measured the morning after 1 day of a 10-mmol sodium diet, during which three oral doses of furosemide were given at 10 a.m., 2 p.m., and 6 p.m. Using this criterion, these researchers found that 51% of hypertensives and 26% of normotensives were sodium-sensitive. They noted that sodium sensitivity displays a typical bell-shaped distribution, with a shift in those who are hypertensive. These investigators observed a further shift with increasing age both in normotensives and, even more markedly, in hypertensives (Weinberger and Fineberg, 1991) (Fig.

3-10).

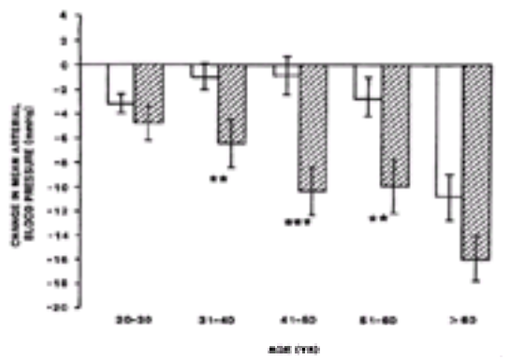

FIG. 3-10. This bar graph shows changes in mean arterial pressure in response to maneuvers used to define salt responsiveness as a function of age in normotensive (open bars) and hypertensive (hatched bars) patients. Brackets represent standard deviation of the mean. Significance values between hypertensive and normal subjects were as follows: **p >.01, ***p >.001. (Reprinted from Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure. Hypertension 1991;18:67–71, with permission.)

Multiple mechanisms for sodium sensitivity have been proposed, including

- A defect in renal sodium excretion manifested by renal vasoconstriction (Schmidlin et al., 1999), and higher rates of proximal sodium reabsorption (Chiolero et al., 2000), are two suggested mechanisms. These may, in turn, reflect a less-than-normal suppression of intrarenal renin release (van Paassen et al., 1996), a paradoxical decrease in atrial natriuretic pep-tide secretion (Campese et al., 1996), less activity of renal kallikrein (Madeddu et al., 1996), or decreased activity of 11b-hydroxy-steroid dehydrogenase-2, increasing glucocorticoid access to mineralocorticoid receptors (Lovati et al., 1999).
- Increased activity of the sodium-hydrogen exchanger in the proximal tubule (Siffert and Düsing, 1995).
- A higher level of sympathetic nervous system (SNS) activity (Miyajima et al., 1999; Okuguchi et al., 1999) and greater pressor reactivity (Campese et al., 1993) than normal.
- Endothelial dysfunction (Bragulat et al., 2001) related to a decreased nitric oxide response to sodium loads (Cubeddu et al., 2000).

The number of proposed mechanisms under-scores the lack of certainty about which of these are involved (Weinberger, 1996). Regardless of how it occurs, greater sodium sensitivity is related to a number of other abnormalities, including

- Insulin resistance (Suzuki et al., 2000)
- Microalbuminuria (Bihorac et al., 2000)
- Lack of nocturnal dipping of BP (Uzu et al., 1996)
- Impaired diastolic function (Musiari et al., 1999)
- Higher rates of mortality (Weinberger et al., 2001)

Despite the widespread belief that volume expansion is more of a factor in blacks than in non-blacks, as is supported by blacks' greater frequency of sodium sensitivity under short-term testing (Weinberger et al., 1986), similar BP responses to salt restriction and loading were noted in a large group of untreated black and nonblack hypertensives (Chrysant et al., 1997). Although sodium sensitivity increases with age (Fig. 3-10), no differences were found between men and women or obese and nonobese individuals.

Whatever the mechanism, sodium sensitivity is likely heritable, with close mother-offspring resemblance in BP change with sodium restriction (Miller et al., 1987). A genetic contribution is further supported by an association with the haptoglobin-1,1 phenotype (Weinberger et al., 1987). Moreover, greater sodium sensitivity has been noted in two populations in those persons who have the 235T allele of the angiotensinogen gene, which is associated with higher blood angiotensinogen levels (Hunt et al., 1999).

RENAL SODIUM RETENTION

With more than enough sodium in the diet and many mechanisms to explain sodium sensitivity, we turn to the evidence that “essential hypertension is due primarily to an abnormal kidney which has an unwillingness to excrete sodium” (de Wardener, 1996). Literally thou-sands of investigators have brought us to our current understanding of the role of the kidneys in primary hypertension. Of these, the hypotheses of four investigators (and their co-workers) will be described: those of Guyton, Laragh, Brenner, and the trio of Dahl, de Wardener, and Blaustein. Although their concepts do not meld into a unifying hypothesis and often are in conflict, a case can be built for what each has pro-posed to be a logical explanation for abnormal renal sodium retention as the initiating event for hypertension. Each of the four hypotheses will now be described.

Resetting of Pressure-Natriuresis

In healthy people, when BP rises, renal excretion of sodium and water increases, shrinking fluid volume and returning the BP to normal— the phenomenon of *pressure-natriuresis* . On the basis of animal experiments and computer models, (Guyton 1961, 1992) considers the regulation of body fluid volume by the kidneys to be the dominant mechanism for the long-term control of BP, the only one of many regulatory controls to have sustained and infinite power. Therefore, if hypertension develops, he reasons that something must be amiss with the pressurenatriuresis control mechanism; otherwise, the BP would return to normal. The evidence has been nicely summarized by Cowley and Roman (1996).

Experimental Support

The concept is based on a solid foundation: When BP is raised, the normal kidney excretes more salt and water—that is, pressure-natriuresis occurs (Selkurt, 1951). The curve relating BP to sodium excretion is steep (Fig. 3-11). A small change in renal perfusion pressure causes a large change in the rate of sodium and water excretion, acting as a powerful negative-feed-back stabilizer of systemic BP. Under normal conditions, the perfusion pressure is approximately 100 mm Hg, sodium excretion is approximately 150 mEq per day, and the two are in a remarkably balanced state. As BP rises, the elevation in renal perfusion pressure leads to a decrease in sodium reabsorption in the proximal tubule (Yip et al., 2000) and, perhaps, in the loop of Henle. As a consequence, body fluid volumes would shrink enough to lower the BP back to its previous level.

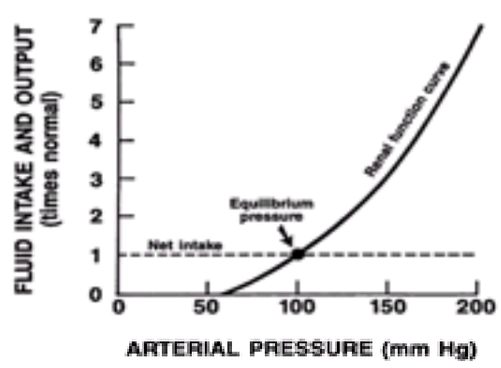

FIG. 3-11. Graphic analysis of arterial pressure regulation by the kidney-fluid volume pressure control system. Pressure continually approaches the point at which the

renal function curve inter-sects the net intake line (i.e., equilibrium pressure). [Reprinted from Guyton AC. Kidneys and fluids in pressure regulation. *Hypertension* 1992; 19(Suppl 1):I2–I8, with permission.]

Resetting of Pressure-Natriuresis

In patients with primary hypertension, as in every genetic form of experimental hypertension, a resetting of the pressure-sodium excretion curve prevents the return of BP to normal (Palmer, 2001). The shift in pressure-natriuresis requires increased BP to maintain fluid balance. As a consequence of the resetting, when BP is lowered by nondiuretic drugs, reactive sodium retention occurs. In a study by Omvik et al. (1980), 12 hypertensive patients were given nitroprusside while sodium excretion was continually monitored. The slope of the pressurenatriuresis curve was directly related to the severity of the hypertension, and less sodium excretion always accompanied the fall in BP. Moreover, in two forms of secondary hypertension—primary aldosteronism and renovascular hypertension—resetting has been shown to shift back toward normal when the hypertension is relieved (Kimura et al., 1987).

As seen in Figure 3-12, Guyton and co-workers have shown that either the entire curve can be shifted to the right or the slope can be depressed, depending on the type of renal insult, which is, in turn, reflected by varying sensitivity to sodium (Hall et al., 1996). Kimura and Brenner (1993) have hypothesized that a rightward shift follows preglomerular (i.e., afferent, arteriolar) vasoconstriction, whereas a depressed slope is the consequence of a decrease in glomerular ultrafiltration or an increase in tubular sodium reabsorption (Table 3-3).

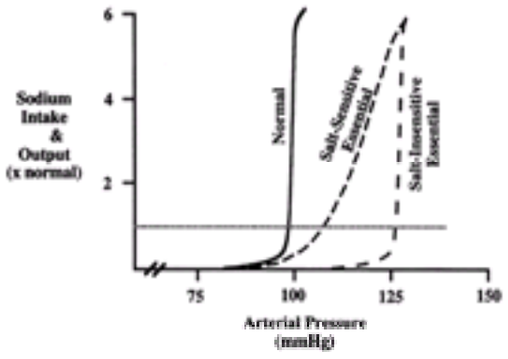

FIG. 3-12. Schematic of steady-state relationships between arterial pressures and sodium excretion (equal to intake) in both salt-sensitive and salt-insensitive essential hypertension. (Modified from Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation. *J Am Soc Nephrol* 1999;10:S258–S265.)

Pressure-natriuresis relationship	Glomerular hemodynamics	Examples of human hypertension
Rightward shift (non-sodium-sensitive)	Preglomerular (afferent arteriolar) vasoconstriction	Renovascular hypertension; essential hypertension
Depressed slope (sodium-sensitive)	Decrease in ultrafiltration coefficient*; increase in tubular sodium reabsorption	Hypertension in blacks, glomerulonephritis, primary aldosteronism, diabetes mellitus

*The ultrafiltration coefficient can be expressed as the product of the number of glomeruli, the glomerular filtration surface area per glomerulus, and the hydraulic conductivity of the glomerular capillary walls.

Reprinted from Kimura G, Brenner BM. A method for distinguishing salt-sensitive from non-salt-sensitive forms of human and experimental hypertension. *Curr Opin Nephrol Hypertens* 1993;2:341–345, with permission.

TABLE 3-3. *Renal mechanisms of hypertension (hypothesis)*

Mechanisms of Resetting

The pressure-natriuresis relationship can be modified by neural and humoral factors including the RAS, sympathetic nervous activity, atrial natriuretic factor, metabolites of arachidonic acid (Moreno et al., 2001), and intrarenal nitric oxide (Majid et al., 2001). The RAS is likely the major modifier (Hall et al., 1999; van Paassen et al., 2000), with an increase in renal sodium reabsorption occurring at concentrations of AII much below those needed for peripheral vasoconstriction. In normotension, RAS is suppressed when sodium intake is increased and stimulated when sodium intake is reduced, allowing sodium excretion to be adjusted without changes in BP. Suppression of RAS by ACE inhibitors (ACEIs) or AII receptor blockers allows sodium excretion to be maintained at reduced BP while decreasing the slope of pressure-natriuresis (i.e., BP becomes sodium-sensitive). Stimulation of the RAS reduces renal sodium excretion and impairs pressure-natriuresis, necessitating a higher BP to maintain sodium balance. Clinically, such persistent stimulation of the RAS is seen in chronic edematous states, such as cirrhosis with ascites, wherein sodium excretion is limited because BP cannot rise from an inability to fill the circulation; the RAS remains elevated despite progressive fluid retention.

In hypertension, as will be noted, RAS activity is “inappropriately normal”; that is, it is not sup-pressed as expected from higher pressure against the juxtaglomerular apparatus. The inappropriately high RAS level reduces renal sodium excretory ability and shifts pressure-natriuresis to the right, necessitating an increased level of BP to maintain sodium balance. The major site of AII's action is on renal tubular sodium reabsorption by direct effects on membrane transport (Hall et al., 1999). Blockade of the RAS in hypertension provides the same benefit as in normotension: A shift back toward normal of pressure-natriuresis so that renal sodium excretion is increased at a lower BP, thereby maintaining sodium balance without an expansion of fluid volume.

Inherited Defect in Renal Sodium Excretion

In certain animal models, the alteration in renal function responsible for the resetting of the pressure-natriuresis curve is inherited. Using rats bred to be either sensitive or resistant to the hypertensive action of dietary sodium, Dahl and Heine (1975) demonstrated the primacy of the kidney in the development of hypertension by a series of transplant experiments. As shown in Figure 3-13, the BP follows the kidney: When a kidney from a normotensive donor was trans-planted to a hypertensive host, the BP of the recipient fell to normal. Conversely, when a hypertensive kidney was transplanted into a normotensive host, the BP rose.

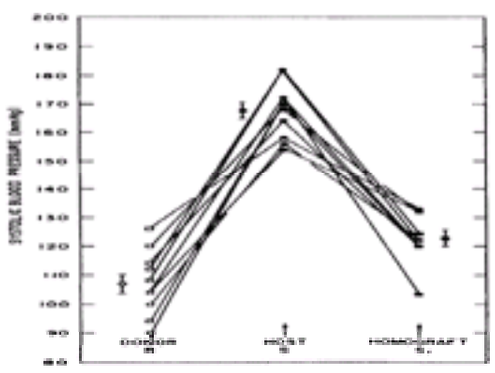

FIG. 3-13. Effect of transplanting “normotensive” kidneys from resistant rats (donor R; *open squares*) to hypertensive sensitive rats (host S; *closed circles*). The resultant blood pressure levels at a median time of 17 weeks after surgery are shown on the right (*closed squares*). The mean blood pressure plus or minus the standard error is indicated for each group. (Reprinted from Dahl LK, Heine M. Primary role of renal homographs in setting chronic blood pressure and levels in rats. *Circ Res* 1975;36:692–696, with permission.)

Evidence in Humans

The possibility of an inherited defect in renal function is supported further by transplantation studies in humans. Curtis et al. (1983) observed long-term remission of hypertension after renal transplantation in six black male patients who likely developed renal failure solely as a consequence of primary hypertension. Because five of these patients had remained hypertensive after removal of their native kidneys, their hypertension was presumably not of renal pressor origin. The most likely explanation for the reversal of hypertension in these patients was the implantation of normal renal tissue, which provided control of body fluid volume, something their original kidneys had been unable to manage. Moreover, hypertension develops more frequently in recipients of renal transplants from hypertensive donors than in recipients from normotensive donors (Guidi et al., 1996).

Nocturia and Natriuresis

A more benign but bothersome aspect of the shift in pressure-natriuresis is nocturia. A reversal of the normal circadian rhythm of urine output occurs with aging and is further accentuated with hypertension. In normotensives, nocturnal urine flow accounts for 53% of urine output in 60- to 80-year-olds as compared to 25% in 25- to 35-year-olds (McKeigue and Reynard, 2000). Hypertensives have even more nocturia (Dyer et al., 1998). Presumably both the age- and BP-related increases in nocturia reflect resetting of the pressure-natriuresis relationship. Fluid retained during the day, accentuated by upright posture (Centonza et al., 2000), is then excreted during the night. Relief should be provided by a morning dose of a diuretic such as hydrochlorothiazide that prevents fluid retention during the day.

Induced Natriuretic Hormone

The Guyton hypothesis allows for a normal or slightly contracted blood volume despite an elevated pressure, in keeping with most volume measurements in hypertensive patients (Harrap et al., 2000). The next hypothesis requires an initially expanded plasma volume that, after an inhibition of renal sodium reabsorption, is allowed to return to normal.

The concept began with another set of Dahl's experiments in rats (Dahl et al., 1967). A chronic parabiotic union was made between sodium-sensitive and sodium-resistant rats. The authors observed that “the animal from the strain that normally fails to develop salt hypertension rap-idly developed chronic hypertension provided that a high NaCl diet was consumed by the pair. This response has been interpreted as being compatible with the transfer of a humoral influence from one parabiotic animal to the other” (Dahl et al., 1967). Soon thereafter, Dahl et al. (1969) provided evidence that this “humoral influence” worked as a “sodium-excreting hormone.”

The search for the nature of this sodium-excreting hormone, made in the salt-sensitive animal and transferred to the salt-resistant one, actually had begun in 1961 when de Wardener et al. showed that plasma from sodium-loaded animals contains a natriuretic substance. In 1976, Haddy and Overbeck proposed that the BP of volume-expanded hypertension was raised by a circulating inhibitor of the Na^+/K^+-ATPase pump. The next year, Blaustein (1977) provided evidence that such an inhibitor could induce hypertension by inhibiting sodium-calcium exchange in vascular tissue, increasing intracellular calcium and thereby raising PR. de Wardener and MacGregor (1980) then suggested that the increase in the sodium transport inhibitor (Dahl's saluretic sub-stance) might be a consequence of an inherited defect in the kidney's ability to excrete sodium.

The search for the natriuretic hormone that arises when plasma volume is expanded, perhaps from an inherited defect in renal sodium excretion, has gone on for more than 30 years (de Wardener, 1996). (This natriuretic hormone is functionally and chemically entirely distinct from the atrial and brain natriuretic peptides that were identified more recently.) Endogenous inhibitors of Na^+/K^+– ATPase pump activity have been found in sodium-sensitive rats (Fedorova et al., 2001), and some believe that ouabain may be the endogenous pump inhibitor (Aperia, 2001). However, Manunta et al. (2001) have provided evidence that ouabain may induce hypertension (in rats) by mechanisms independent of the sodium pump.

Although some investigators doubt the presence and significance of ouabain as the endogenous digitalis-like inhibitor of the sodium pump (Nicholls et al., 1995; (Tao et al., 1997), the weight of current evidence favors its role Aperia, 2001). In keeping with the experimental evidence that ouabain increases intracellular sodium and thereby mobilizes calcium from intracellular stores (Borin et al., 1994), Blaustein (1996) has formulated an overall scheme for this acquired compensatory mechanism for renal sodium retention, which could be a cause of primary hypertension (Fig. 3-14).

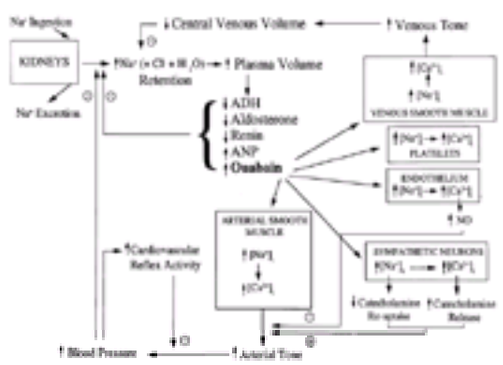

FIG. 3-14. Diagram showing various feedback loops that may be involved in the rise in blood pressure that accompanies the attempt to prevent plasma volume expansion when excessive sodium is ingested relative to the innate ability of the kidneys to excrete a sodium load. The increase in intracellular sodium is the direct result of the inhibition of the Na^+ pump by ouabain; the increase in intracellular calcium then is mediated by the Na^+/Ca^{2+} exchanger as a result of the rise in sodium. Å, positive-feedback loop; ⊖, negative-feedback loop; ADH, antidiuretic hormone; ANP, atrial natriuretic peptides; $[Ca^{2+}]$, intracellular calcium concentration; $[Na^+]$, intracellular sodium concentration. (Reprinted from Blaustein MP. Endogenous ouabain: role in the pathogenesis of hypertension. *Kidney Int* 1996;49:1748–1753, with permission.)

As will be covered later in this chapter, numerous other defects in sodium and calcium transport and intracellular binding have been postulated to be involved in the pathogenesis of hypertension.

Renin and Nephron Heterogeneity

For more than 40 years, Laragh (2001a) has explored the RAS, adding immensely to our understanding of both the mechanisms and treatment of hypertension. As part of these labors, Sealey et al. (1988) have provided another hypothesis for the renal contribution to the pathogenesis of primary hypertension, based on the presence of “. . . a subpopulation of nephrons that is ischemic from either afferent arteriolar vasoconstriction or from an intrinsic narrowing of the lumen. Renin secretion from this subgroup of nephrons is tonically elevated. This increased renin secretion then interferes with the compensatory capacity of intermingled normal nephrons to adaptively excrete sodium and, consequently, perturbs overall blood pressure homeostasis.”

This hypothesis is similar to that proposed by Goldblatt (1958), who believed that “the primary cause of essential hypertension in humans is intrarenal obliterative

vascular disease, from any cause, usually arterial and arteriolar sclerosis, or any other condition that brings about the same disturbance of intrarenal hemodynamics." Although investigators were unable to place minuscule clamps on small arterioles, Goldblatt's experimental concept nonetheless is the basis for the more modern model pro-posed by Sealey et al. (1988) (Table 3-4). The elevated renin levels from the ischemic population of nephrons, although diluted in the systemic circulation, become the "normal" renin levels that are usual in patients early in the course of primary hypertension (Harrap et al., 2000), in whom suppression of renin secretion and demonstration of low circulating levels would otherwise be expected. The diluted levels are still high enough to impair sodium excretion in the nonischemic hyperfiltering nephrons but are too low to support efferent tone in the ischemic nephrons, thereby reducing sodium excretion in them as well.

There are ischemic nephrons with impaired sodium excretion intermingled with adapting hyperfiltering hypernatriuretic nephrons.
Renin secretion is high from ischemic nephrons and low from hyperfiltering nephrons.
The inappropriate circulating renin-angiotensin level impairs sodium excretion because
In the adapting hypernatriuretic nephrons
It increases tubular sodium reabsorption.
It enhances tubuloglomerular feedback–mediated afferent constriction.
As the circulating renin level is diluted by nonparticipation of adapting nephrons, it becomes inadequate to support efferent tone in hypoperfused nephrons.
A loss of nephron number with age and from ischemia further impairs sodium excretion.

Reprinted from Sealey JE, Blumenfeld JD, Bell GM, et al. On the renal basis of essential hypertension. *J Hypertens* 1988;6:763–777, with permission.

TABLE 3-4. *Hypothesis: There is nephron heterogeneity in essential hypertension*

Sealey et al. (1988) expanded their model to explain the varying plasma renin levels seen both in healthy individuals at different ages and in patients with primary hypertension as well as the high renin levels seen with renovascular hypertension and the low renin levels seen with primary aldosteronism. Even the low-renin form of primary hypertension presumably involves a few ischemic nephrons, because "*any* renin secretion in the presence of arterial hypertension is abnormal and it works in the same way to impair salt excretion and raise BP" (Sealey et al., 1988).

Additional discussion of the multiple roles of the RAS will come later in this chapter, after we review the last of the four models for renal sodium retention.

Reduced Nephron Number

Brenner et al. (1988) have proposed that hyper-tension may arise from a congenital reduction in the number of nephrons or in the filtration surface area per glomerulus, thereby limiting the ability to excrete sodium, raising the BP, and setting off a vicious circle whereby systemic hypertension begets glomerular hypertension, which begets more systemic hypertension (Brenner and Chertow, 1994) (Fig. 3-15). These investigators point out that as many as 40% of individuals younger than 30 years have fewer than the presumably normal number of nephrons (600,000 per kidney) and "speculate that those individuals whose con-genital nephron numbers fall in the lower range constitute the population subsets that exhibit enhanced susceptibility to the development of essential hypertension." Similarly, a decrease in filtration surface area, reflected in a decreased glomerular diameter or capillary basement membrane surface area, may be responsible for an increased susceptibility to hypertension even in the presence of a normal nephron number.

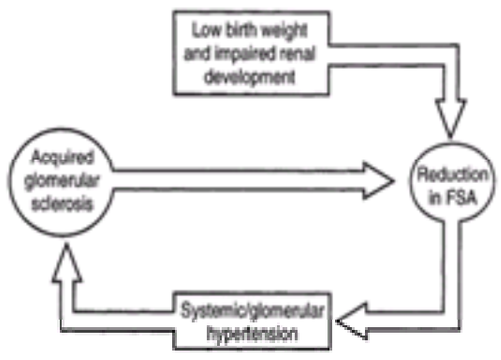

FIG. 3-15. A diagram of the hypothesis that the risks of developing essential hypertension and progressive renal injury in adult life are increased as a result of congenital oligonephropathy, or an inborn deficit of filtration surface area (FSA), caused by impaired renal development. (Modified from Brenner BM, Chertow GM. Con-genital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 1994;23:171–175.)

Brenner and Anderson (1992) invoke this con-genital decrease in filtration surface as a possible explanation for observed differences in susceptibility to hypertension among certain populations such as in blacks, women, and older people, all of whom may have smaller kidneys or fewer functioning nephrons than other populations. As is described in Chapter 9, these investigators have developed a similar hypothesis for the progression of renal damage that is commonly observed among diabetics and patients with most forms of acquired kidney disease (Brenner and Mackenzie, 1997).

Low Birth Weight

The low-birth-weight hypothesis has received considerable support from the growing evidence that BP in adult life is inversely related to birth weight: The smaller is the baby from intrauterine growth retardation, the higher the BP and risk of cardiovascular disease in later life (Law and Shiell, 1996) (Fig. 3-16). The relationship is demonstrable during childhood and adolescence (Lurbe et al., 2001), and nearly all the data from the 21 studies summarized in Figure 3-16 show lower systolic BP with each kilogram increase in birth weight. An association has been claimed between restricted fetal growth (intrauterine growth retardation or low birth weight for gestational age) and coronaryheart disease, type 2 diabetes, dyslipidemia, suicide, and (as will be noted) chronic renal disease. In brief, poor maternal nutrition is said to influence adversely development of the fetal pancreas, liver, kidney, and vasculature, thereby programming the low-birth-weight infant to later diseases.

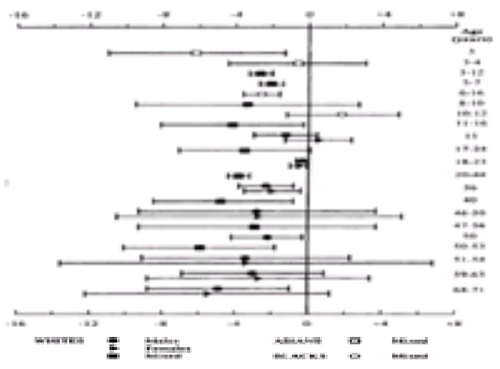

FIG. 3-16. Difference in systolic blood pressure (mm Hg) per kilogram increase in birth weight according to age, gender, and race in 21 studies arranged in descending order of current age. Symbols show the regression coefficient for birth weight from the regression of systolic blood pressure on birth weight and current size (weight in children, body mass index in adults). Horizontal bars show the 95% confidence intervals. *Solid circles*, white males; *solid triangles*, white females; *solid squares*, white males and females; *open squares*, Asian males and females; *open circles*, black males and females. (Reprinted from Law CM, Shiell AW. Is blood

pressure inversely related to birth weight? *J Hypertens* 1996; 14:935–941, with permission.)

There are, however, an increasing number of questions about the neatness of this construct, widely referred to as the *fetal origins* or *Barker hypothesis* (after Professor David Barker, who has been its leading proponent) (Barker, 1998). One is the finding that fetal malnutrition, as during famines, does not lead to more adult diseases (Stanner et al., 1997). Another comes from studies on twins: Although some researchers find that the smaller twin has higher BP (Leon, 1999), others report that this does not hold true for monozygotic twins (Ijzerman et al., 2000), so that genetic factors presumably play an important role. Moreover, the relation may be coincidental, not causal: Hypertensive men and women, whose children are more likely to inherit hypertension-inducing genes, are more likely to give birth to small babies (Walker et al., 1998). Similarly, genetically determined insulin resistance results in impaired insulin-mediated growth in the fetus as well as insulin resistance in adult life (Hattersley and Tooke, 1999).

Obviously, low birth weight often reflects lower socioeconomic status which, in itself, is associated with more hypertension, diabetes, and coronary disease. And even if the association is causal, the rather small differences in adult BP found with fairly large differences in fetal weight suggest a minor overall impact on public health (Kramer, 2000).

Rather than birth weight, more rapid growth during childhood (as would be expected in babies who are small at birth) has been found to be a stronger determinant of adult BP (Falkner et al., 1998). In some studies, the associations with low birth weight have emerged only when adult weight has been adjusted or only among obese adults (Leon et al., 1996), further supporting a role for postnatal rather than prenatal factors (Lucas et al., 1999). Therefore, although there are concerns about poor maternal nutrition, the prevention of obesity by overfeeding during child-hood and later life seems far more important for the prevention of hypertension, diabetes, and coronary disease.

Congenital Oligonephropathy

Various mechanisms for the apparent relationship between low birth weight and adult hypertension have been proposed, including excess exposure of the fetus to maternal glucocorticoids (Seckl, 1997), resulting in altered control of cortisol secretion in adult life (Reynolds et al., 2001) and impaired endothelial function (Martin et al., 2000). The most likely mechanism is congenital oligonephropathy: Fewer nephrons as a result of intrauterine growth retardation (Mackenzie and Brenner, 1995). As first documented by Hinch-liffe et al. (1992) and confirmed by Konje et al. (1996), most nephrogenesis occurs in the last 6 to 8 weeks of human gestation, and growth retardation during that period limits nephron development. The reduced number of nephrons at birth in low-birth-weight neonates (Mañalich et al., 2000) cannot be replenished later, despite excellent postnatal nutrition (Lucas and Morley, 1994). The subsequent scenario has been described by Mackenzie and Brenner (1995):

> Deficiencies in the total nephron supply, by limiting total renal excretory capacity and thereby influencing the point at which steady-state conditions between BP and sodium excretion are achieved, could profoundly affect long-term BP regulation. When renal mass is greatly reduced, as in the case of extensive experimental ablation of the kidney in rodents, BP increases in the systemic arterial circulation and in the glomerular capillaries, thus increasing glomerular filtration rate and promoting fluid excretion. However, sustained elevations in glomerular capillary hydraulic pressure are associated with the development of focal and segmental glomerular sclerosis leading to further loss of nephrons and a self-perpetuating vicious cycle of hypertension and progressive glomerular injury. . . . Given the association between low birth weight and fewer nephrons . . . it is naturally tempting to speculate that the origins of hypertension in adults who were of low birth weight lie in a deficient endowment of nephrons secondary to intrauterine growth retardation.

In rats, as in humans, a low-protein diet during pregnancy induces oligonephropathy and hypertension in the offspring (Vehaskari et al., 2001). A reduction in sodium intake (Kreutz et al., 2000) and postnatal administration of an ACEI or an AII receptor blocker (Sherman and Langley-Evans, 2000) prevented the development of hypertension in such offspring.

Clinical Implications

Low birth weight has been correlated with increased prevalences of chronic renal disease among Australian Aborigines (Hoy et al., 1999) and people in South Carolina (Lackland et al., 2000). In addition, the greater prevalence of hypertension among blacks has been attributed to their greater likelihood of having low-birth-weight babies (Lopes and Port, 1995). Multiple factors likely contribute to this greater likelihood: More teenage pregnancies (Spitz et al., 1996), shorter intervals between pregnancies (Zhu et al., 1999), inadequate nutrition and social deprivation because of poverty (Strobino et al., 1995), familial aggregation (Wang et al., 1995), a higher prevalence of chronic hypertension (Haelterman et al., 1997) and preeclampsia (Ødegård et al., 2000), and other unknown factors linked to the U.S. black population (David and Collins, 1997). Of interest, despite comparable socioeconomic deprivation, U.S. Hispanic women do not appear to have a higher number of low-birth-weight babies (Buekens et al., 2000).

The opportunity for overcoming most of these contributing factors is obvious but has not yet proved to be effective (Klerman et al., 2001). However, recent cutbacks in support for teenage contraception, maternal nutrition, and prenatal care in the United States suggest that we will continue to pay billions for the eventual care of hypertension-related end-stage renal disease, strokes, and heart attacks instead of millions for preventive care of the disadvantaged.

An Adaptation to Growth

Another view of the relation between BP and renal function has been provided by Weder and Schork (1994). Having observed an intimate linkage in rats between somatic growth and BP (Schork et al., 1994), these investigators "pro-pose that blood pressure rises during childhood to subserve homeostatic needs of the organism," specifically renal function. They believe that because modern diet and lifestyle stimulate earlier and greater somatic growth, rising BP is a necessary, but also eventually harmful, compensation for maintaining renal function.

Their hypothesis can be viewed as the body's response to the pressure-natriuresis relationship and the inability to expand the number of nephrons postnatally: As more sodium is ingested and more demands are placed on the fixed renal capacity, higher BP is needed to maintain natriuresis and overall renal excretory function. Hypertension is the unfortunate price paid to preserve homeostasis.

Now that numerous mechanisms for renal sodium retention have been demonstrated, we will return to an examination of the RAS.

RENIN-ANGIOTENSIN SYSTEM

More than 100 years since the discovery of renin by Tigerstedt and Bergman (Phillips and Schmidt-Ott, 1999), our knowledge of the many roles of the RAS continues to expand (Nicholls and Robertson, 2000). Figure 3-17 is a schematic overview of the RAS, showing its major components, the regulators of renin release, and the primary effects of AII, excluding the AII receptors. In addition, several degradation products of AII may have biologic functions (Ardaillou, 1997).

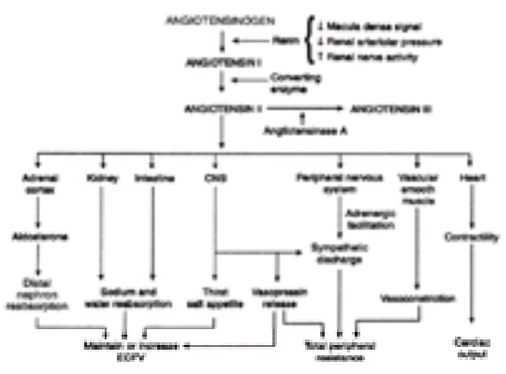

FIG. 3-17. Schematic representation of the renin-angiotensin system, showing the major regulators of renin release, the biochemical cascade leading to angiotensin II, and the major effects of angiotensin II. CNS, central nervous system; ECFV, extracellular fluid volume.

Properties and Control of Renin

Renin is stored and secreted from the renal juxtaglomerular cells located in the wall of the afferent arteriole, which is contiguous with the macula densa portion of the same nephron (Schnermann and Briggs, 1999). The multiple factors that can alter renin secretion include those shown in Figure 3-17, with changes in pressure within the afferent arterioles and sodium concentration in the macula densa likely playing the most important roles.

Expression and regulation of the human renin gene and the structure of the enzyme have been elucidated (Bader and Ganten, 2000). The molecular biology of the RAS has been found to be increasingly more complicated than was once believed (Kim and Iwao, 2000).

Prorenin

The first product of the translation of renin messenger RNA is preprorenin, which is processed in the endoplasmic reticulum to the 47-kDa prorenin. Although prorenin constitutes 80% to 90% of the renin in human plasma (Danser et al., 1996), its physiologic or pathogenic role has not yet been established. Prorenin does not seem to be converted within the circulation into active renin, but such conversion may occur within tis-sues (Hsueh and Baxter, 1991). High concentrations are present in ovarian follicular fluid (Itskovitz et al., 1991), and high plasma prorenin levels are present in type 1 diabetics, particularly in those with microvascular complications (Wilson and Luetscher, 1990).

Sealey and co-workers have presented an imaginative scheme for an active *vasodilatory* role for prorenin, believing that it acts as a balance to the vasoconstrictive effects of renin-AII (Halimi and Sealey, 1992). Thus, high levels of vasodilatory prorenin could contribute to the hyperperfusion seen in diabetes mellitus, whereas high levels of renin would explain the ischemic vascular injury of high-renin hypertensive states.

Extrarenal Renin-Angiotensin

The RAS acts within both the circulation and various tissues. Most workers in this field now accept the presence of a functional cardiac RAS (de Mello and Danser, 2000; Dostal and Baker, 1999). Although most cardiac renin is likely derived from plasma renin of renal origin (Katz et al., 1997), most cardiac AII is likely produced within the heart by conversion of locally synthesized rather than blood-derived angiotensin I (AI) (van Kats et al., 1998).

Renin may be synthesized in the adrenal cortex (Mulrow, 1998), and there is evidence for local generation of AII in tissues (Saris et al., 2000).

Components of the System

Renin acts as an aspartyl proteinase that catalyzes the hydrolytic release of the decapeptide AI from its a-globulin substrate, angiotensinogen (Fig. 3-17). Renin itself probably is without effect other than by its generation of AI.

Angiotensinogen

The amount of the renin substrate(angiotensinogen) in the plasma may vary considerably, and its level may play some role in the overall function of the RAS (Bohlender et al., 2000). Estrogens and other stimulators of hepatic microsomal enzyme activity will increase renin substrate levels. As noted earlier in this chapter, high levels of plasma angiotensinogen have been found in people genetically predisposed to develop hypertension (Watt et al., 1992).

Angiotensin-Converting Enzyme

The two end–amino acids, histidyl and leucine, of AI are removed, forming the 8–amino acid polypeptide AII, by a converting enzyme present in plasma but mainly bound to tissues (Esther et al., 1997). Conversion occurs throughout the body, particularly in the lung (Erdös, 1990).

Chymase

Chymase, a serine protease that also converts AI to AII, has been identified in various sites but particularly in the heart (C-C Wei et al., 1999) and arteries (Richard et al., 2001). Obviously, the presence of an ACE-independent pathway could support additional benefits of AII receptor blockers over ACEIs (see Chapter 7).

Angiotensin Activity

Most, if not all, of the effects of the RAS are mediated by the 8–amino acid AII, but angiotensin-(1-7) may be a modulator of the system (Roks et al., 1999).

Angiotensin Receptors

In a manner comparable to that of other peptide hormones, the action of AII is triggered by its interaction with receptors on the plasma membrane of the tissues responsive to the hormone. Two receptors have been cloned, one [AII type 1 receptor (AT_1)] of which has two isoforms (Davisson et al., 2000) and apparently mediates virtually all the known effects of AII (Good-friend et al., 1996).

Considerable effort has been directed at the possible role of the AII type 2 receptor (AT_2) receptor, which is expressed in low concentrations in kidney, heart, and mesenteric blood vessels (Carey et al., 2001). Activation of the AT_2 receptor likely stimulates vasodilation via bradykinin and nitric oxide and perhaps has other effects that oppose those of activation of the AT_1 receptor.

Actions of Angiotensin II

As shown in Figure 3-17, AII acts not only on vascular smooth muscle and the adrenal cortex but also within the heart, kidneys, and central and autonomic nervous systems. These actions amplify its volume-retaining and vasoconstrictive effects on the peripheral vascular system. Figure 3-3 indicates that AII may be involved in all four of the primary stimuli to both CO and PR.

Beyond these effects, AII induces cell growth and hypertrophy independent of its effect on BP (Su et al., 1998). Moreover, AII appears to induce an inflammatory response in vascular smooth muscle cells (Kranzhöfer et al., 1999), with activation of nuclear factor k-B (Luft, 2001) and adhesion molecule-1 expression (Tummala et al., 1999), which may serve as direct links to atherosclerosis.

Effects of Inhibition of Renin-Angiotensin

Figure 3-18 shows the four sites at which interruption of the RAS is now feasible. The mechanisms by which agents can act to inhibit the system will be covered in detail in Chapter 7, along with practical considerations about their use to treat hypertension and its complications.

FIG. 3-18. The four sites of action of the currently available inhibitors of the renin-angiotensin system. CE, conversion enzyme; J-G, juxtaglomerular cells.

Evidence derived from these inhibitors has helped to define the role of the RAS in primary hypertension. This role will be examined after a brief review of the measurements of these hormones.

Plasma Renin Activity

Although direct assays of plasma AII (Simon et al., 1992) and renin (Hurwitz et al., 2001) are available, plasma renin activity (PRA) usually is measured by incubating a patient's plasma, which contains both angiotensinogen and renin, to generate AI, which then is measured by radioimmunoassay (Sealey et al., 1995). The amount of AI generated is proportional to the amount of renin present.

Considering all the factors affecting the level of renin, the agreement noted in the literature is rather surprising: Almost all patients with primary aldosteronism have suppressed values, most patients with renovascular or accelerated malignant hypertension have elevated levels, and the incidence of suppressed values among patients with primary hypertension is surprisingly similar in different series (Fig. 3-19). Specific information about the use of PRA assays in the evaluation of various identifiable forms of hypertension is provided in subsequent chapters.

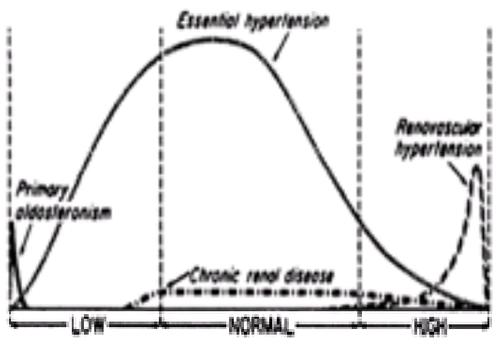

FIG. 3-19. Schematic representation of plasma renin activity in various hypertensive diseases. The approximate number of patients with each type of hypertension is indicated along with their proportion of low, normal, or high renin levels. (Reprinted from Kaplan NM. Renin profiles. *JAMA* 1977;238:611–613. Copyright 1977, American Medical Association, with permission.)

The listing in Table 3-5 is not intended to cover every known condition and disease in which a renin assay has been performed, but the more clinically important ones are listed in an attempt to categorize them by mechanism. Some conditions could fit in two or more categories; for example, upright posture may involve a decreased effective plasma volume, a decreased renal BP, or catecholamine excess.

TABLE 3-5. *Clinical conditions affecting plasma renin activity (PRA)*

Role in Primary Hypertension

In keeping with the effects of higher perfusion pressure at the juxtaglomerular cell and the high-normal blood volume seen in primary hypertension, suppression of renin release and low levels of PRA are expected. In fact, patients with primary hypertension tend to have lower PRA levels than do age- and gender-matched normotensives (Helmer, 1964;Meade et al., 1983). However, the majority of patients with primary hypertension do not have low, sup-pressed renin-angiotensin levels, stimulating a large amount of clinical research to explain the “inappropriately” normal or even elevated PRA levels seen in most patients (Fig. 3-19). Two logical explanations have been presented: the proposal of Sealey et al. (1988) of nephron heterogeneity, with a population of ischemic nephrons contributing excess renin (as described earlier in this chapter), and Julius's (1988a) concept of a state of increased sympathetic drive (explored later in this chapter).

Nonmodulation

A third explanation for inappropriately normal renin levels has been proposed by Williams GH et al. (2000) on the basis of a series of studies indicating that as many as half of normal-renin and high-renin hypertensive patients have defective feedback regulation of the RAS within the kidney and the adrenal glands.

Normal Modulation

Normal individuals modulate the responsiveness of their AII target tissues with their level of dietary sodium intake: With sodium restriction, the adrenal secretion of aldosterone is enhanced, and vascular responses are reduced; with sodium loading, the adrenal response is sup-pressed, and vascular responses are enhanced, particularly within the renal circulation. With sodium restriction, renal blood flow is reduced, facilitating sodium conservation; with sodium loading, renal blood flow is increased, promoting sodium excretion. These changes are mediated mainly by changes in tissue responsiveness to AII, increasing with sodium restriction and

decreasing with sodium loading.

Abnormal Modulation

Williams, Hollenberg, and their co-workers have found that approximately one-half of normal- to high-renin hypertensives are *nonmodulators*, as characterized by abnormal adrenal and renal responses to AII infusions and salt loads (Williams GH et al., 2000). These findings have been attributed to an abnormally regulated and rather fixed level of tissue AII that, in the adrenal tissues, does not increase aldosterone secretion in response to sodium restriction and, in the renal circulation, does not allow renal blood flow to increase with sodium loading. The hypothesis that there is an abnormally regulated, fixed local AII concentration in these nonmodulators received support from the correction of both the adrenal and renal defects after suppression of AII by ACEIs. Moreover, an association of nonmodulation with the TT variant of the angiotensinogen gene was found (Hopkins et al., 1996).

Nonmodulation in the face of relatively high dietary sodium intake could help to explain the pathogenesis of sodium-sensitive hypertension and provide a more targeted, rational therapy for its correction. However, sodium restriction in sodium-sensitive nonmodulators could be counterproductive if it further increases the already high degree of insulin resistance in such persons (Raji et al., 2001). A lower prevalence of non- modulation has been found in young women, suggesting that female sex hormones may confer protection against this genotypic predisposition to hypertension (Fisher et al., 1997). GH Williams et al. (2000) suggest that estrogen could modify the defect in the regulatory region of the angiotensinogen gene that sometimes is seen in nonmodulators.

Other investigators have documented non-modulation in hypertensives (Ferri et al., 1994; Ozono et al., 1996). However, in the largest study yet reported, involving 287 non-Hispanic white adults in whom renal plasma flow in response to AII infusion was measured, there was only a weak relationship between the renal response to AII and BP levels, explaining less than 10% of the variation in BP (Turner and Kardia, 1997).

Primary Hypertension with Low Renin

Clearly, there are numerous possible explanations for normal levels of renin in hypertension, which is the usual finding. Although low renin levels are expected in the absence of one or another of the previously described circumstances (Laragh, 2001b), a great deal of work has been done to uncover special mechanisms, prognoses, and therapy for hypertensives with low renin, in particular for the twofold greater prevalence of low renin in blacks than in non-blacks (Sagnella, 2001).

Mechanisms

One of the possible mechanisms for low-renin hypertension is volume expansion with or with-out mineralocorticoid excess, but the majority of careful analyses fail to indicate volume expansion (Sagnella, 2001) or increased levels of mineralocorticoids (Pratt et al., 1999). In keeping with normal levels of aldosterone despite the low renin levels, low-renin hypertensives showed a lesser rise in aldosterone secretion on a low-sodium diet, similar to that previously described in nonmodulating patients (Fisher et al., 1999).

As described in chapter 13 and chapter 14, new forms of low-renin hypertension have recently been recognized, one with increased amounts of 18-hydroxylated steroids, the other with high levels of cortisol from inhibition of the 11b-hydroxy-steroid dehydrogenase enzyme. Not surprisingly, subtle degrees of these defects have been looked for in low-renin hypertensives, with only equivocal results (Soro et al., 1995; Rossi et al., 2001). There is evidence for the presence of a mutation in the epithelial sodium channel (ENaC), as is responsible for Liddle's syndrome (see Chapter 13): Among black hypertensives in London, 8.3% had a heterozygous T594M mutation of the ENaC, as compared to 2.1% of the black normotensives (Baker et al., 1998). Several lines of evidence for higher ENaC activity in blacks than in whites have been noted that could contribute to blacks' greater tendency for sodium retention and, thereby, greater risk for hypertension (Ambrosius et al., 1999).

Prognosis

A retrospective analysis over a 7-year interval showed that patients with low-renin hypertension had no strokes or heart attacks, whereas 11% of normal-renin and 14% of high-renin patients had experienced one of these cardiovascular complications (Brunner et al., 1972). High renin levels most likely indicate more severe intrarenal vascular damage, so that the higher rate of complications among the high-renin group is not surprising. However, the data of Brunner et al. posed the possibility of vasculotoxic effects of presumably normal levels of renin.

Although a number of subsequent studies failed to document an improved prognosis in low-renin hypertension (Birkenhäger et al., 1977; Kaplan, 1975), Alderman et al. (1991) prospectively tested the prognostic value of the renin-sodium profile in 1,717 hypertensive subjects followed up for as long as 8 years while being treated. The incidence of myocardial infarction was 14.7 per 1,000 person-years in the 12% with high renin levels, 5.6 per 1,000 person-years in the 56% with a normal level, and 2.8 per 1,000 person-years in the 32% with a low renin level. The incidence of stroke was not correlated with renin status, but the association with heart attack remained significant after adjustment for various possible confounders. In an expanded population followed up for as long as 3.6 years, the relation between PRA levels and myocardial infarction remained independent and direct, but only in those with an initial BP above 95 mm Hg (Alderman et al., 1997).

Conversely, Meade et al. (1993) found no association between PRA levels and ischemic heart disease in a 20-year follow-up of 803 white, normotensive men. Similarly, total plasma renin concentration was not found to be a risk factor for coronary disease in a 4.9-year prospective study of white men (Singh et al., 2000), and no increase in carotid artery disease was found among high-renin patients (Rossi et al., 2000). Some have noted direct relation between renin levels and left ventricular hyper-trophy (Aronow et al., 1997; (Koga et al., 1998), whereas others have not (Vakili et al., 2000).

Therapy

In keeping with their presumed but unproved volume excess, patients with low-renin primary hypertension have been found by some investigators (Vaughan et al., 1973; Preston et al., 1998, but not by others Ferguson et al., 1977; Holland et al., 1979; Hunyor et al., 1975), to experience a greater fall in BP when given diuretics than do normal-renin patients.

If low-renin hypertensive patients do respond better to diuretics, the response does not necessarily indicate a greater volume load. Patients with low renin, by definition, are less responsive to stimuli that increase renin levels, including volume depletion, and they therefore experience a lesser rise in PRA with diuretic therapy. This would result in less compensatory vasoconstriction and aldosterone secretion, so that volume depletion would proceed and the BP would fall farther in low-renin hypertensive patients given a diuretic than in those with greater renin responsiveness.

Despite the attractiveness of basing therapeutic choices on the renin profile (Blumenfeld and Laragh, 1998), age and race were better predictors of response to various drugs (Preston et al., 1998) and, in some studies, the renin status simply did not reflect the response at all (Weir and Saunders, 1998).

Summary

Although low renin levels are expected in primary hypertension, the presence of normal or high levels in most patients has generated a search for an involvement of such inappropriate levels in the pathogenesis of the disease. It seems likely that this mechanism is abnormally activated in many patients with primary hyper-tension, and at least three mechanisms have been offered: nephron heterogeneity, nonmodulation, and increased sympathetic drive.

Laragh (1973,2001b) and co-workers have long attached a great deal of significance to the various PRA levels found in patients with primary hypertension. According to this view, the levels of renin can identify the relative contributions of vasoconstriction (PR) and body fluid volume expansion to the pathogenesis of hypertension. According to the “bipolar vasoconstriction-volume analysis,” arteriolar vasoconstriction by AII is predominantly responsible for the hypertension in patients with high renin, whereas volume expansion is predominantly responsible in those with low renin.

As imaginative and logical as this construct may be, in clinical practice most practitioners have not found renin profiling to be necessary for establishing prognosis or determining therapy. As will be noted, renin profiling is often used in the diagnosis of low- and high-renin forms of hypertension.

STRESS AND OVERACTIVITY OF THE SYMPATHETIC NERVOUS SYSTEM

As shown in Figure 3-3, an excess of renin and angiotensin activity could interact with the SNS to mediate most of its effects. In contrast, stress may activate the SNS directly; and SNS overactivity, in turn, may interact with high sodium intake, the RAS, and insulin resistance, among other possible mechanisms. Considerable evidence supports increased SNS activity in early hypertension (Esler et al., 2001) and, even more impressively, in the still-normotensive offspring of hypertensive parents, among whom a large number are likely to develop hypertension.

Before considering further some of the evidence, a brief review of the pertinent physiology of the SNS will be provided.

Normal Physiology

Figure 3-20 shows the two major neural reflex acts that are involved in the regulation of BP: the high-pressure baroreceptors of the aortic arch and carotid sinus and the low-pressure cardiopulmonary baroreceptors (Rea, 1993). After the afferent signals enter the vasomotor center in the brainstem, efferent impulses traverse the parasympathetic and sympathetic nerves to the heart and vasculature. As seen in Figure 3-21, sympathetic nerves and their catecholamine secretions induce their effects by multiple inter-actions with both presynaptic and postsynaptic receptors (Weinshilboum, 1999).

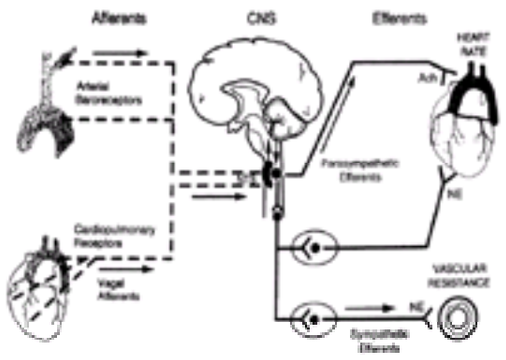

FIG. 3-20. The two major neural reflex acts (arterial baroreceptors and cardiopulmonary baroreceptors) involved in blood pressure regulation. Ach, acetylcholine; CNS, central nervous system; NE, norepinephrine; NTS, nucleus tractus solitarius. (Reprinted from Rea RF. Cardiopulmonary barore- flexes and central blood volume. In: Izzo JL, Black HR, Taubert TA, eds. Hypertension primer. Dallas: American Heart Association, 1993;71–72, with permission.)

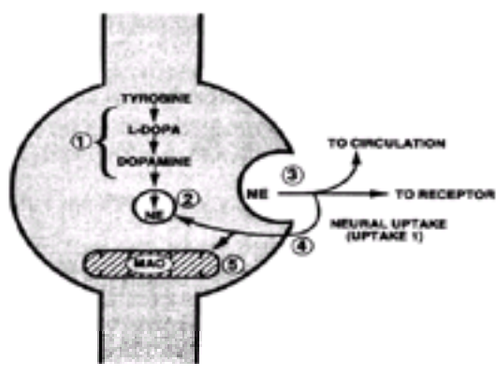

FIG. 3-21. A prototypic adrenergic nerve terminal is shown, with various processes regulating catecholamines.Œ, biosynthesis; , storage; Ž, release; , uptake; , metabolism. MAO, monoamineoxidase; NE, norepinephrine. (Reprinted from Weinshilboum R. Catecholamine synthesis, release,and update. In: JL Izzo, HR Black, eds. Hypertension primer, 2nd ed. Dallas: American Heart Association,1999;7–10, with permission.)

Baroreceptor Dysfunction

The arterial baroreflex rapidly buffers acute fluctuations in BP, as during changes in posture or stress. By vascular distension, an increase in BP is transduced into electrical activity, triggering reflex parasympathetic activation and sympathetic inhibition, so that heart rate is slowed and vascular resistance decreased, buffering the rise in BP. Conversely, baroreceptor activity decreases when BP falls, producing reflex-mediated increases in heart rate and PR (Chapleau et al., 2001). Marked BP variability is seen in patients with baroreceptor denervation (Sleight, 2001).

Baroreceptor activity is reset during sustained increases in BP, but the reset baroreceptors still buffer changes in BP so that most hypertensives maintain normal baroceptor sensitivity. However, the resetting of baroreflex plays at least a permissive role in the perpetuation of inappropriately elevated sympathetic activity in established hypertension (Izzo and Taylor, 1999).

Furthermore, baroreceptor insensitivity or blunting, manifested as a diminished change in heart rate as BP changes, often occurs in long-standing hypertension, presumably from arteriosclerotic stiffness of the large arteries wherein the receptors are located. The decreased baroreceptor sensitivity permits elevated BP to remain high while, if severe, simultaneously leading to the propensity to postural hypotension often seen in elderly patients with systolic hypertension (see Chapter 4). Impaired baroreflex heart rate response likely participates in the left ventricular diastolic dysfunction often seen in hypertensives (Pitzalis et al., 1999).

Certainly in heart failure and likely in hyper-tension, baroreflexes may be inappropriately active (Izzo and Taylor, 1999). As shown in Figure 3-22, Shepherd (1990) has proposed that decreased inhibition of the vasomotor center resulting from the resetting of the arterial baroreceptors (mechanoreceptors) may be involved in increased sympathetic outflow and thereby the perpetuation of hypertension.

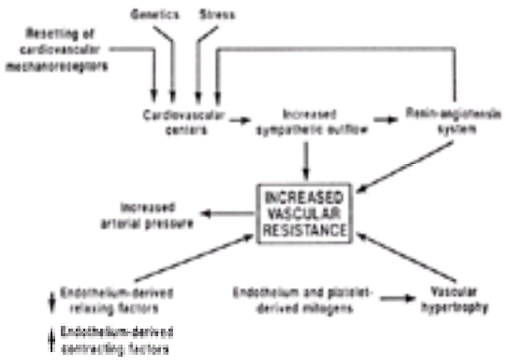

FIG. 3-22. Indications that an increased sympathetic outflow may be a key factor in primary hyper-tension. The outflow is increased when arterial baroreceptors are reset so that they exert less inhibition on the vasomotor center. The resetting could be due to genetic changes in the endothelial lining of the carotid sinus and aortic arch or at the vasomotor centers. The increased sympathetic outflow may be further enhanced by stress. As a consequence of this neurohumoral excitation, the systemic vascular resistance is increased. In addition, the endothelial cells in the resistance blood vessel may secrete less vasodilator and more vasoconstrictor substances, thus compounding the vasoconstriction. Furthermore, mitogens produced in endothelial cells and also released from platelets, together with norepinephrine, can cause proliferation of the vascular smooth muscle, with further aggravation of the systemic vasoconstriction. [Reproduced from Shepherd JT.

Increased systemic vascular resistance and primary hypertension. *J Hypertens* 1990;8(Suppl 7):S15–S27, with permission.]

Brainstem Compression

Experimentally, lesions of the nucleus tractus solitarius in the medulla produce a labile form of hypertension in rats. A connection between the experimental and clinical evidence has been claimed by PJ Janetta et al. (1985) and others (Naraghi et al., 1994) who have per-formed vascular decompression of looping arteries at the lateral aspect of the medulla. Further coverage of this contentious issue is provided in Chapter 6.

Role of Stress

As shown in Figure 3-22, SNS overactivity could lead to hypertension, and stress is an obvious stimulant of the SNS. Let us examine the claim that hypertensives and, even more important, those likely to develop hypertension either experience more stress or respond differently to stress.

Exposure to Stress

Multiple studies suggest that people exposed to repeated psychogenic stresses may develop hypertension more frequently than would other-wise similar people who are not as stressed:

- As an extreme example, the BP remained normal among nuns in a secluded order over a 30-year period, whereas it rose with age in women living nearby in the outside world (Timio et al., 1999).
- Air traffic controllers, who work under high-level psychological stress, annually develop hypertension at a rate 5.6 times greater than that of nonprofessional pilots who were initially comparable to the controllers in physical characteristics (Cobb and Rose, 1973). However, no differences in ambulatory BP were seen between 80 air traffic controllers in Milan and age-matched men in a nearby town (Sega et al., 1998).
- Among healthy employed men, job strain (defined as high psychological demands and low decision latitude on the job) is associated with higher awake ambulatory BP, an increased risk for developing hypertension, and an increased left ventricular mass index by echocardiography (Pickering, 1997), at least partly mediated by an increased heart rate in response to stress (Vrijkotte et al., 2000).
- Exposure to higher noise levels at work also is associated with a higher BP (Tomei et al., 2000).
- Multiple populations living in small, cohesive, protected societies have been found to have low BPs that do not rise with aging, whereas individuals who abandon such an environment and migrate to more urbanized, modern, disorganized societies have higher BPs that do rise with age (Kaufman et al., 1996; Poulter et al., 1990). Environmental factors such as weight gain and increased sodium intake may be responsible, but there is considerable evidence that social disorganization, as would be expected with migration, is associated with more hypertension (Bland et al., 1991).
- The relatively high prevalence of hypertension among blacks has been attributed to their increased level of anger and social stresses (Shapiro et al., 1996); however, blacks may not be unique in this regard: Whites in the lower social classes (Tyroler, 1989), who are more anxious (Markovitz et al., 1993), who are unemployed (Brackbill et al., 1995), or who have less formal education (Stamler et al., 1992) also experience more hypertension and the higher mortality associated with it than do whites in the upper social classes.

Reactivity to Stress

Even healthy young people display transient endothelial dysfunction after mental stress (Ghiadoni et al., 2000). However, greater cardiovascular and SNS reactivities to various laboratory stresses have been documented in hypertensives and in normotensives at higher risk for developing hypertension (Markovitz et al., 1998; Saab et al., 2001; Steptoe and Cropley, 2000), extending even to a greater anticipatory BP response while awaiting an exercise stress test (Everson et al., 1996).

Some investigators, however, do not find increased responses to laboratory stresses among the offspring of hypertensives (de Visser et al., 1995; Manuck et al., 1996). Although the evidence for a different psychological substrate in prehypertensive people is impressive, it should be remembered that most of the data are short-term, cross-sectional observations that may not relate to the underlying pathogenesis of hypertension. Julius et al. (1991b) found that hyperreactivity to mental stress was seen more often in the offspring of hypertensive parents but that such hyperreactivity was unrelated to the future development of hypertension. In particular, there is a need to study patients' reactivity before they are aware of their diagnosis, as they may display increases in various measures of SNS activity in response to mental stress after becoming aware of their diagnosis (Rostrup et al., 1991) or as a result of an alerting reaction to the examinations (Palatini et al., 1996).

Nonetheless, numerous studies show a greater intensity of anger and hostility but, at the same time, a greater suppression of the expression of anger among hypertensives (Schneider et al., 1986), patients whose BP rises over time (Perini et al., 1991), and normotensive offspring of hypertensive parents (Perini et al., 1990). Such normotensive offspring more often have a greater pressor response to a_2-adrenergic receptor blockade (Dao et al., 1998).

Part of the explanation for the inconsistent findings of an enhanced pressor response to laboratory stress as a predictor of future hypertension may be the failure to consider both the genetic predisposition to hypertension and the level of life stress. In a 10-year follow-up of 103 young men, Light et al. (1999) found the highest rises in BP over time among those who responded most to laboratory stresses and who also had a positive family history of hypertension and were exposed to higher levels of daily stress.

Obviously, stress and hypertension are not always connected in isolation. As Pickering (1997) writes:

> There is emerging evidence that the various stimuli that lead to hypertension are not independent of each other, but tend to interact in clusters. Thus exposure to stress may not only raise BP itself, but also lead to increased alcohol and fat intake. A final common pathway for many of these factors is the sympathetic nervous system, which is involved in the development of essential hypertension in its early stages, and in the hypertensive effects of salt, obesity, physical inactivity, and possibly stress as well.

Role of Epinephrine

A mechanism exists for the translation of intermittent stress into more sustained hypertension. The adrenomedullary secretion of epinephrine may induce far greater and longer effects on the BP than does the relatively short fight-or-flight response. After an infusion of epinephrine at levels comparable to those seen during stress, the BP rose and remained elevated for some time thereafter (Blankestijn et al., 1988). Presumably, part of the epinephrine entered the sympathetic nerve endings and was re-released into the synaptic cleft during subsequent stimulation of the sympathetic nerves. In addition, epinephrine acts on the presynaptic b_2-receptor to facilitate the release of more norepinephrine. Cardiac norepinephrine spillover was higher in hypertensives and was correlated directly to the release of epinephrine (Rumantir et al., 2000a). As Esler et al. (2001) note: “These data provide perhaps the most direct evidence to-date in support of the 'adrenaline hypothesis' of essential hypertension.”

Faulty Norepinephrine Reuptake

Esler and co-workers have found also an impairment of the neuronal reuptake of norepinephrine (site 4 in Fig. 3-21) in essential hypertensives (Rumantir et al., 2000b). Such a defect could expose the target cells to higher levels of norepinephrine, amplifying the neural signals of sympathetic nervous activity.

Renal Effects of Sympathetic Activity

Hypertensive patients decrease renal sodium excretion in response to mental stress (Schneider et al., 2001). This may occur through stimulation of renal sympathetic nerves. Di Bona (2000) has summarized his and his co-workers' extensive studies of the role of renal sympathetic nerves as a “differentiated regulation of various organs.” They have shown that increases in renal SNS activity sequentially increase renin secretion first, then decrease urinary sodium excretion by increasing renal tubular sodium reabsorption and, finally, decrease renal blood flow and glomerular filtration rate. He concludes, “With dysregulation of renal sympathetic nerve activity, the renal functional effects contribute importantly to the underlying pathophysiology, e.g., in congestive heart failure or hypertension.”

Changes with Age

Various indices of sympathetic nerve hyperreactivity are seen exclusively or mainly in younger patients, including higher plasma levels of nor-epinephrine and norepinephrine spillover (Ferrier et al., 1993), augmented muscle sympathetic nerve activity (Floras and Hara, 1993), and increased epinephrine release (Jacobs et al., 1997). Julius (1990) explains the tendency for previously elevated plasma norepinephrine levels to fall as hypertension becomes established by a negative feedback of the elevated BP per se on the central nervous system. This same explanation is offered for the transition from a high CO to an elevated vascular resistance. As stated by Julius and Nesbitt (1996):

> As hypertension escalates, the hemodynamic pattern changes from a high cardiac output to a high resistance pattern. This hemodynamic change is best explained by an alteration in the structure and responsiveness of the heart and blood vessels. Decreased cardiac compliance and diminished b-adrenergic responsiveness tend to decrease cardiac output, whereas the development of vascular hypertrophy increases vascular resistance. In parallel, the sympathetic tone is down-regulated, since, with emerging vascular hyperresponsiveness, less sympathetic drive is needed to maintain the elevated blood pressure.

Summary

These various pieces of evidence add up to make a fairly strong case for a role of increased SNS activity in the pathogenesis of hypertension (Brook and Julius, 2000; Esler et al., 2001). This role may be even greater in magnitude when hypertension and obesity coexist, as they so often do (Grassi et al., 2000). Therefore, catecholamines are leading candidates to be both the pressor mechanism that initiates the rise in BP and the trophic mechanism that maintains hypertension via vascular hypertrophy (Yu et al., 1996).

Whatever the specific role of SNS activity in the pathogenesis of hypertension, it appears to be involved in the increased cardiovascular morbidity and mortality that afflicts hypertensive patients during the early morning hours. Epinephrine levels begin to increase after awakening and norepinephrine rises sharply on standing (Dodt et al., 1997). As a consequence of the increased SNS activity, BP rises abruptly and markedly and, as detailed in Chapter 2, this rise is at least partly responsible for the increase in sudden death, heart attack, and stroke during the early morning hours.

Increased sympathetic activity likely is responsible also for the increased heart rate present in many hypertensives that previously was noted to be associated with increased cardiovascular mortality.

PERIPHERAL RESISTANCE

The preceding sections have covered the major elements that could induce hypertension primarily by increasing CO. Although many variables can influence CO, the preceding discussion of fluid volume and myocardial contractility seems adequate to explain the primary mechanisms. However, when we turn to the second part of the equation BP = CO ¥ PR, the situation becomes inherently more complicated. The multiple factors affecting PR that are shown in Figure 3-3 make up only a superficial listing of what may be involved. As shown in Figure 3-23, vascular tone is determined by multiple factors, even more than are shown in this scheme. For example, shear stress has short- and long-term effects on vascular tone, and the ways by which shear stress is translated into various endothelial responses involve multiple mediators (Malek et al., 1999).

FIG. 3-23. Regulation of vascular tone by perivascular nerves and endothelial cells. Neuropeptide (NPY), noradrenaline (NA), adenosine triphosphate (ATP), substance P (SP), calcitonin gene– related peptide (CGRP), and vasoactive intestinal peptide (VIP) from nerve varicosities in the adventitia act on receptors in the media, causing vasoconstriction (+) or vasodilation (–). ATP, acetylcholine (ACh), 5-hydroxytryptamine (5-HT), and SP, released from endothelial cells by shear stress or hypoxia, act on their receptors on endothelial cells to release endothelium-derived relaxing factor (EDRF; nitric oxide) or prostaglandins (PG), which, in turn, induce smooth muscle relaxation. Angiotensin II (ATII), vasopressin (VP), and histamine (H) are also contained in, and may be released from, subpopulations of endothelial cells. a, adrenoreceptor; M, muscarinic receptor; P_{2x}, purinoceptors. (Reprinted from Dowd P. Raynaud's phenomenon. *Lancet* 1995;346:283–290, with permission.)

Causes and Consequences

Beyond the complexities of what may influence PR is a fundamental problem: The major consequences of hypertension afflict the larger-capacitance arteries, which are also the only ones that can be directly visualized and easily studied; however, the major cause of hypertension— elevated PR—resides in the distal resistance arteries and arterioles, with diameters of less than 1 mm, whose contribution can be studied only by biopsy and *in vitro* techniques (Park et al., 2001). Therefore, most of the literature covers the larger arteries, both because they are more easily studied and because they are involved in the major complications induced by hypertension.

Another caveat is in order: Changes in vascular structure and function may be either the cause or the consequence of elevated BP. For instance, even acute rises in BP disturb endothelial function (Millgård and Lind, 1998), but endothelial dysfunction clearly can be responsible for rises in BP.

The atherosclerotic and arteriosclerotic con-sequences of hypertension are addressed in the next chapter. Here, however, as the role of PR in the pathogenesis of hypertension is considered, we should not lose sight of the primacy of the microcirculation in the genesis and maintenance of hypertension (Pries et al., 1999). This contribution of the microcirculation may involve even the capillary bed, because capillary rarefaction is present early in the course of hypertension (Antonios et al., 1999) and even in normotensive offspring of hypertensive parents (Noon et al., 1997). These findings suggest either genetic or fetal influences on small–blood vessel growth (Struijker Boudier, 1999).

Vascular Changes in Hypertension

Hypertension, however it begins, is maintained by increased PR, largely due to decreased arterial lumen size or radius. According to Poiseuille's law, vascular resistance is positively related to both the viscosity of blood and the length of the arterial system and negatively related to the third power of the luminal radius. Because neither viscosity nor length is much, if at all, altered, and because small changes in the luminal radius can have a major effect, it is apparent that the increased vascular resistance seen in established hypertension must reflect changes in the caliber of the small resistance arteries and arterioles (Folkow et al., 1970). In studies of small resistance vessels from subcutaneous tissue of hypertensive subjects as compared to normotensives, increases in the ratio of media thickness to internal diameter of 26% to 62% have been recorded (Heagerty et al., 1993; Park et al., 2001). Because of the increased wall thickness–lumen diameter ratio, higher wall stress and intraluminal pressure develop when resistance vessels are stimulated.

Remodeling

The changes in the ratio of media thickness to luminal radius in hypertension involve a combination of two processes, defined as eutrophic remodeling and hypertrophic remodeling (Mulvany, 1999) (Fig. 3-24). In eutrophic remodeling, as found in early primary hypertension, the outer diameter and the lumen are

decreased, whereas the cross-sectional area of the media is unaltered, resulting in an increase in the media-lumen ratio (Fig. 3-24, c). Such structural changes have been seen in early, mild hypertension, followed in frequency by endothelial dysfunction and, finally, cardiac hypertrophy (Park and Schiffrin, 2000).

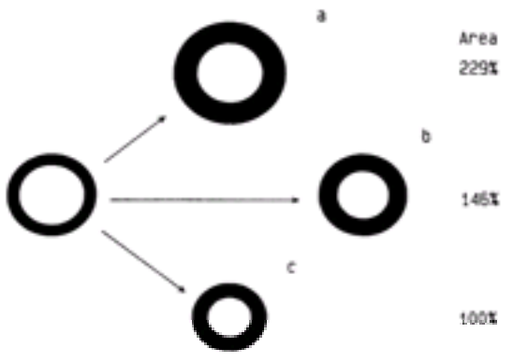

FIG. 3-24. Different modes of structural changes of arteries. The silhouette on the left shows the media cross section of the control vessel. On the right are various ways in which the media thickness–lumen diameter ratio can be doubled. **A:** Material has been added to the outer surface (hypertrophic outward remodeling). **B:** Material has been added to the inner surface (hypertrophic inner remodeling). **C:** There has been rearrangement of the existing material, with a consequent reduction in lumen diameter (eutrophic inner remodeling). The percentages on the right show the relative cross-sectional areas. (Reprinted from Heagerty AM, Aalkjaer C, Bund SJ, et al. Small artery structure in hypertension. *Hypertension* 1993;21:391–397, with permission.)

Mulvany (1995) concludes that “the changes in the structure of the resistance vasculature that are seen in hypertension can account for the altered hemodynamic characteristics. The evidence points against the structural changes being due mainly to a growth response (unlike conduit arteries, where there is good evidence for vascular growth in essential hypertension).”

Such remodeling could be purely an adaptive response to the BP that has been elevated through some other mechanism. Mulvany (1995), however, believes that there is strong evidence that factors other than BP determine resistance-vessel structure. For instance, the infusion of subpressor doses of AII into rats leads to remodeling, even when hydralazine was also given to prevent a subsequent rise in BP (Griffin et al., 1991). Moreover, in humans, treatment with an ACE I causes a greater reduction in media-lumen ratio than does a b-blocker, despite equal antihypertensive efficacy (Schiffrin et al., 1995).

Large-Vessel Hypertrophy

Unlike the apparent eutrophic remodeling process in smaller resistance vessels, hypertrophic remodeling (Fig. 3-24, a) clearly develops in larger arteries as an early manifestation of essential hypertension (Tice et al., 1996), with close symmetry between vascular and cardiac hypertrophy (Roman et al., 2000; Vaudo et al., 2000). Moreover, in small resistance arteries of patients with renovascular hypertension exposed to high levels of AII, hypertrophic remodeling was much more obvious than in patients with essential hypertension, in whom eutrophic remodeling was predominant (Rizzoni et al., 1996).

In keeping with this finding, much of our cur-rent knowledge about vascular hypertrophy has come from the study of certain forms of endocrine hypertension, including pheochromocytoma, primary aldosteronism, and renovascular disease. Each of these secondary forms of hyper-tension is known to arise from the direct effect of a specific pressor hormone. What has now become obvious is that, regardless of the initial hormonal effect, whether it be volume retention (as with primary aldosteronism) or vasoconstriction (as with pheochromocytoma or renovascular disease), maintenance of hypertension derives from vascular hypertrophy that increases PR. As summarized by Lever and Harrap (1992):

> Most forms of secondary hypertension have two pressor mechanisms; a primary cause, e.g., renal clip, and a second process, which is slow to develop, capable of maintaining hypertension after removal of the primary cause, and probably self-perpetuating in nature. We suggest that essential hypertension also has two mechanisms, both based upon cardiovascular hyper-trophy: 1) a growth-promoting process in children (equivalent to the primary cause in secondary hypertension); and 2) a self-perpetuating mechanism in adults.

Sustaining Hypertrophic Response

As seen in Figure 3-25, Lever and Harrap (1992) start with the original proposal of Folkow (1990), wherein hypertension is initiated by a minor overactivity of a specific fast-acting pressor mechanism (e.g., AII) that raises BP slightly and initiates a positive feedback loop that induces vascular hypertrophy and maintains the hypertension. The amplification (or feedback loop) is “slowly progressive, ultimately large and probably nonspecific. Thus different forms of chronic hypertension may resemble each other because part of the hyper-tension in each has the same mechanism” (Lever, 1986). In the second and third hypotheses, two other elements are added: a genetically determined, reinforced hypertrophic response and the direct contribution of one or more trophic mechanisms for hypertrophy.

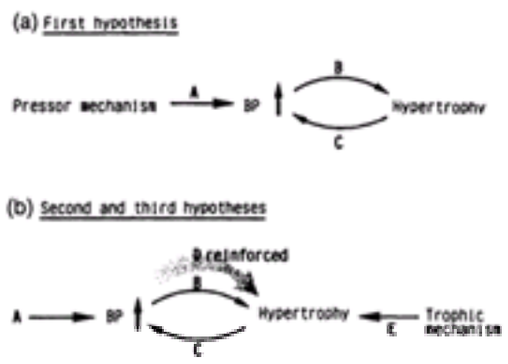

FIG. 3-25. Hypotheses for the initiation and maintenance of hypertension. **A:** Folkow's first proposal that a minor overactivity of a pressor mechanism (A) raises blood pressure (BP) slightly, initiating positive feedback (B to C to B) and a progressive rise in blood pressure. **B:** Second and third hypotheses, which are similar to the first, with two additional signals: an abnormal or “reinforced” hypertrophic response to pressure (D) and an increase of a humoral agent (E) that causes hypertrophy directly. (Reproduced from Lever AF, Harrap SB. Essential hypertension: a disorder of growth with origins in childhood? *J Hypertens* 1992;10:101–120, with permission.)

This scheme, involving both an immediate pressor action and a slow hypertrophic effect, may be common to the action of various pressor-growth promoters. In the majority of hypertensive patients, no marked excess of any of the known pressor hormones is identifiable. Nonetheless, a lesser excess of one or more may have been responsible for initiation of the process that is sustained by the positive feedback postulated by Folkow (1990) and the trophic effects emphasized by Lever and Harrap (1992). This sequence encompasses a variety of specific initiating mechanisms that accentuate and maintain the hypertension by a nonspecific feedbacktrophic mechanism. If this double process is involved in the pathogenesis of primary hyper-tension, as seems likely, the difficulty in recognizing the initiating, causal factor is easily explained. In the words of Lever (1986):

> The primary cause of hypertension will be most apparent in the early stages; in the later stages, the cause will be concealed by an increasing contribution from hypertrophy. . . . A particular form of hypertension may wrongly be judged to have “no known cause” because each mechanism considered is insufficiently abnormal by itself to have produced the hypertension. The cause of essential hypertension may have been considered already but rejected for this reason.

Mechanisms of Vascular Change

The mechanisms that generate the narrowed lumen size of hypertension can involve either structural remodeling or a functional increase in vascular tone. In addition, increased mechanical stiffness of arteries occurs, attributable both to structural and functional changes (Bussy et al., 2000), which will be addressed separately. These structural vascular changes “may be caused or influenced by the expression and/or topographic localization of extracellular matrix components, such as collagen and elastin, and by changes in cell-extracellular fibrillar attachment sites, such as adhesion molecules like integrin” (Intengan and Schiffrin, 2000). These dynamic processes occur at variable rates and at different stages during the evolution of hyper-tension (Touyz, 2000).

The functional changes that increase vascular tone may involve both enhanced vasoconstriction in response to pressor stimuli and impaired vasodilation in response to agents that stimulate nitric oxide (NO). Whereas increased pressor responsiveness was examined frequently in the past, most recent work has measured the impairment of vasodilation in response to reactive hyperemia or NO generation (John and Schmieder, 2000). Not surprisingly, the two processes often interact: Systemic infusion of norepinephrine inhibits NO-mediated forearm vasodilation (Millgård and Lind, 1998). Furthermore, functional changes can mediate structural changes: The decreases in NO that occur in response to severe reductions in blood flow promote smooth muscle cell proliferation (Ueno et al., 2000).

Recognizing the fact that these mechanisms must interact in the dynamic processes control-ling BP, brief consideration will be given to some of the major humoral and mechanical factors that influence the vasculature.

Humoral Factors

As shown in Figure 3-26, a number of vasoactive agents, growth factors, and cytokines may be involved in the vascular changes in hypertension (Touyz, 2000). As noted earlier in this chapter, the RAS acts as a vasoconstrictor, growth promoter, and stimulant of synthesis of the extracellular matrix. Endothelin-1 is another humoral vasoconstrictor that likely comes primarily from within the endothelium, as do prostaglandin H_2 and thromboxane A_2 (Ungvari and Koller, 2000). These as well as the primary endothelium-derived relaxing factor, NO, are addressed in the section Endothelium-Derived Vasoactive Substances.

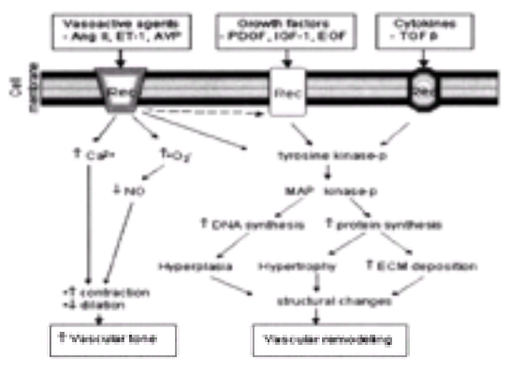

FIG. 3-26. Humoral factors that regulate vascular smooth muscle cell function and growth. Vasoactive agents, growth factors, and cytokines bind to specific receptors (Rec) leading to signaling events that modulate vascular smooth muscle cell contraction and growth. ↑, Increase; ¯, decrease; Ang II, angiotensin II; AVP, arginine vasopressin; ECM, extracellular matrix; EGF, epidermal growth factor; ET-1, endothelin-1; IGF-1, insulinlike growth factor-1; MAP, mitogen-activated protein; NO, nitric oxide; P, phosphorylation; PDGF, platelet-derived growth factor; TGF b, transforming growth factor–b. (Reproduced from Touyz RM. Molecular and cellular mechanisms regulating vascular function and structure—implications in the pathogenesis of hypertension. *Can J Cardiol* 2000;16:1137–1146, with permission.)

Growth Factors and Cytokines

As shown in Figure 3-26, a steadily growing number of growth factors and cytokines have been identified that are mitogenic for vascular smooth muscle cells and may also be involved in the genesis of vascular changes seen in hypertension (Touyz, 2000). These are normally present in low, often undetectable levels but are increased in the vessel wall after vascular injury. Insulinlike growth factor-1 is involved in the mitogenic actions of AII, and cytokines such as transforming growth factor– b_1 regulate both tone and growth of vascular smooth muscle cells.

Mechanical Factors

The luminal, endothelial surface of blood vessels constantly is exposed to hemodynamic shear stress which, in turn, actively influences vessel wall remodeling (Malek et al., 1999). In particular, atherosclerotic lesions have long been known to occur near vascular branching points, apparently as a consequence of low, not high, shear stress just beyond bifurcations. Short-term effects of variations in hemodynamic shear stress from variations in flow increase secretion of prostacyclin and NO. In hypertension, the mechanical strain on the arterial media increases up to 15%, whereas shear forces are little altered with normal CO (Touyz, 2000).

ENDOTHELIUM-DERIVED VASOACTIVE SUBSTANCES

Most of the effects of the various humoral and mechanical factors that control vascular function and structure work through the endothelium, the source of a host of mediators listed in Table 3-6 that maintain a balance of opposing physiologic and pathologic effects (Calles-Escandon and Cipolla, 2001). By the release of a variety of relaxing and contracting factors shown in Figure 3-27, endothelial cells regulate vascular tone and reactivity (Cosentino and Lüscher, 2001). These opposing factors often work simultaneously: Endothelin-1 contributes to the regulation of vascular tone by stimulating NO activity (Cardillo et al., 2000).

Functional targets	Specific cellular or physiologic action	
Lumen	Vasoconstriction	Vasodilation
	Endothelin	*Nitric oxide*
	Angiotensin II	*Bradykinin*
	Thromboxane A_2	*Hyperpolarizing factor*
	Prostaglandin H_2	
Growth	Stimulation	Inhibition
	Platelet growth-derived factor	*Nitric oxide*
	Fibroblast growth factor	*Prostaglandin I_2*
	Insulinlike growth factor-1	*Transforming growth factor*
	Endothelin	
	Angiotensin II	
Inflammation	Proinflammatory	Antiinflammatory
	Adhesion molecules (ELAM, VCAM, ICAM)	
Hemostasis	Prothrombotic	Antithrombotic
	Plasminogen activator inhibitor	*Prostacyclin*
		Tissue plasminogen activator

ELAM, endothelial leukocyte adhesion molecule; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule.
Note: Mediators are listed in italics.
Modified from Calles-Escandon J, Cipolla M. Diabetes and endothelial dysfunction. Endocr Rev 2001;22:36–52.

TABLE 3-6. *Endothelial cell functions*

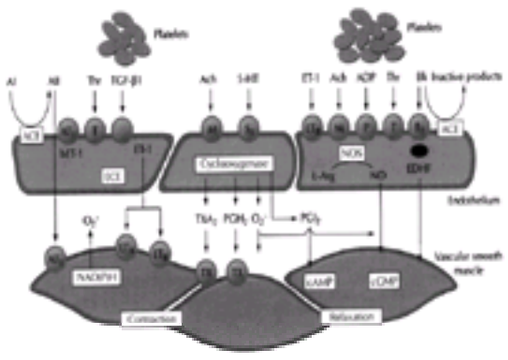

FIG. 3-27. Endothelium-derived vasoactive substances: several circulating and platelet-derived sub-stances can activate specific receptors (*open circles*) on the endothelial membrane to release relaxing factors such as nitric oxide (NO), prostacyclin (PGI2), and a hyperpolarizing factor (EDHF). Endothelium-derived contracting factors are also produced, including endothelin-1 (ET-1), angiotensin II (AII), thromboxane A_2 (TXA_2), and prostaglandin H_2 (PGH_2). AI, angiotensin I; ACE, angiotensin-converting enzyme; Ach, acetylcholine; ADP, adenosine phosphate; bET, big endothelin; Bk, bradykinin; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanine monophosphate; ECE, endothelin-converting enzyme; 5-HT, 5-hydroxytryptamine (serotonin); NOS, nitric oxide synthase; O2–, superoxide anion; TGF-b1, transforming growth factor–b1; Thr, thrombin. (Reproduced from Cosentino F and Lüscher TF. Effects of blood pressure and glucose on endothelial function. *Curr Hypertens Rep* 2001;3:79–88, with permission.)

Nitric Oxide

In 1980, Furchgott and Zawadzki showed that, in vessels constricted by norepinephrine, the normal relaxing response to acetylcholine was abolished if the endothelial lining was rubbed off, depriving the cells of an endothelium-derived relaxing factor. Seven years later, Palmer et al. (1987) identified the endothelium-derived relaxing factor as NO, now known to be the primary endogenous vasodilator. The synthesis of NO is controlled by the enzyme endothelial NO synthase and is induced by calcium-mobilizing agents and fluid shear stress (Govers and Rabelink, 2001). The intravascular half-life of NO is approximately 2 milliseconds, but its extravascular half-life is up to 2 seconds, depending on tissue oxygen concentration (Thomas et al., 2001).

Physiologic Role

NO has been characterized as the perfect messenger (Madison, 1993): fast, because it is not stored in vesicles; short-lived; easily passable through and between cells; and economically produced from an abundant and recyclable substrate. In addition, it uses ubiquitous regulatory machinery (e.g., guanylate cyclase). Basal generation of NO keeps the arterial circulation in an actively dilated state (Vallance, 1998). When the inhibitor of NO synthesis, *N*-monomethyl-Larginine, is infused, BP rises (Rees et al., 1989). Beyond its major role in controlling the cardiovascular system, NO is a principal factor involved in the antiatherosclerotic properties of the endothelium, inhibiting platelet–vessel wall interaction, endothelial permeability, and proliferation of vascular smooth muscle cells (Cosentino and Lüscher, 2001).

NO has multiple other functions on neural, immunologic, and other homeostatic mechanisms (Moncada and Higgs, 1995). Not the least of these may be its role in initiating the smooth muscle relaxation in the corpus cavernosum that permits penile erection (Rajfer et al., 1992).

Pathologic Role

Under basal conditions, whole-body NO production is diminished in patients with essential hypertension (Forte et al., 1997), and impaired NO release may play a role in hypertension and atherosclerosis that develop with aging, hypercholesterolemia, diabetes, homocystinemia, smoking, and physical inactivity. With few exceptions (Cockcroft et al., 1994), hypertensives have been shown to have an impaired vasodilative response (usually measured as fore-arm blood flow) to NO stimulants (usually acetylcholine) but not to endothelium-independent vasodilators such as nitroprusside, as first reported by Panza et al. (1990) and Linder et al. (1990). The impairment, also demonstrated by ultrasonography in response to reactive hyperemia (Iiyama et al., 1996), may reflect more than just reduced synthesis of NO (Kelm et al., 1996; Panza et al., 1995) but is not related to decreased availability of substrate (Panza et al., 1993).

A higher frequency of a missense variant of the endothelial NO synthase gene has been found in hypertensives in Japan (Miyamoto et al., 1998). This evidence for a role of defective NO-mediated vasodilation in the pathogenesis of hypertension has been further strengthened by its recognition in the still-normotensive children of hypertensive parents (McAllister et al., 1999; Taddei et al., 1996). However, the fact that even transient rises in BP significantly impair endothelium-dependent vasodilation (Millgård and Lind, 1998); (Paniagua et al., 2000) raises the fundamental question: Is defective endothelium-dependent vasodilation that is mediated by NO the cause or the consequence of hypertension?

As seen in Figure 3-27, among the contracting factors that can be released from the endothelium is superoxide anion, which can act directly or scavenge NO to form the very powerful oxidant peroxynitrite (Cosentino and Lüscher, 2001). The enzyme superoxide dismutase converts the super-oxide anions to H_2O_2, which may also be a vasorelaxant (Vanhoutte, 2001).

Oxidative stress and subsequent breakdown of NO may be responsible for much of the endothelial dysfunction of hypertension (Hamilton et al., 2001). Large amounts of the antioxidant vitamin C will improve endothelium-dependent vasodilation (Sherman et al., 2000), as will usual doses of inhibitors of the RAS (Hornig et al., 2001).

Effects of Therapy

Drugs that contribute NO, such as nitroglycerin, have been the cornerstone of antianginal therapy for centuries, and nitroprusside is the most potent antihypertensive agent. As of now, long-acting NO donors for treatment of hypertension are not available but are under investigation (Al-Sa'doni and Ferro, 2000).

Variable effects of various classes of antihypertensive drugs on endothelium-dependent vasodilation have been reported (Spieker et al., 2000). In their review, Taddei et al. (2000) conclude:

> The most convincing results are available for calcium entry blockers, which can restore endothelium-dependent vasodilation in different vascular beds . . . by a mechanism possibly related to antioxidant activity. ACE inhibitors . . . improve endothelial function in subcutaneous, epicardial, and renal circulation, whereas they are ineffective in potentiating the blunted response to acetylcholine in the forearm of patients with essential hypertension. ACE inhibitors can selectively improve endothelium-dependent vasodilation to bradykinin, an effect probably mediated by a hyperpolarizing factor and not by restoration of NO availability. Although AT-1 [angiotensin type 1] receptor antagonists can restore endothelium-dependent vasodilation to acetylcholine in subcutaneous micro-circulation but not in the forearm muscle, they can improve basal NO release and decrease the vasoconstrictor effect of endogenous endothelin-1.

Aging, Hypercholesterolemia, and Diabetes

A striking, progressive reduction in endotheliumdependent vasodilation with increasing age has been seen in cross-sectional studies of both normotensive and hypertensive patients (Gerhard et al., 1996); (Taddei et al., 1995).

Hypercholesterolemia, in addition to promoting atherosclerosis, may aggravate hyper-tension by impairing vasodilation, as seen in coronary arteries (Cohen et al., 1988) and fore-arm resistance vessels (Creager et al., 1990). Lipid-lowering therapy has been shown to restore bioavailability of NO (John and Schmeider, 2000), an effect that occurs with statins even without lowering of blood lipid levels (Wilson et al., 2001).

Diabetes may engender its vascular havoc through impaired endothelial function (Calles-Escandon and Cipolla, 2001; Cosentino and Lüscher, 2000). It is likely that every major cardiovascular risk factor may work, at least in part, through endothelial dysfunction (Glasser et al., 1996).

Other Vasodilators

In the excitement over NO, the roles of other putative relaxing factors, shown in Figure 3-27, are seldom mentioned. Prostacyclin and a still-unidentified endothelium-derived hyperpolarizing factor may also be involved (Brandes et al., 2000).

Endothelin

The left of Figure 3-27 shows a number of endothelium-derived contracting factors. Of these, endothelin has been increasingly emphasized since its discovery in 1988 (Yanagisawa et al., 1988). Now known to be composed of four distinct peptides, the endothelins have been shown to have a wide range of biologic actions that may involve them in numerous pathologic conditions (Lüscher and Barton, 2000; (Schiffrin, 2001). Endothelin-1 is the predominant endotheliumderived isoform, exerting its major vascular effect—vasoconstriction and cell proliferation— through activation of specific endothelin A receptors on vascular smooth muscle cells. In contrast, endothelin B receptors mediate vasodilation by stimulation of NO release (Spieker et al., 2000).

When systemic endothelin receptor blockers were given to normotensive patients, peripheral vasodilation and hypotension developed, sup-porting a physiologic role for endothelin-1 in maintenance of peripheral vascular tone and BP (Haynes et al., 1996). The contribution of endothelin to hypertension remains uncertain, but high plasma levels have been reported in hypertensives, even higher in blacks than whites (Ergul, 2000). Hypertensives have an increased vasoconstrictor response to endothelin, which likely reflects increased local availability of the hormone (Cardillo et al., 1997). Moreover, in some hypertensive patients, enhanced endothelial expression of the endothelin-1 gene has been seen in small resistance arteries, suggesting a possible role in vascular hypertrophy (Schiffrin et al., 1997).

As effective endothelin blockers become available, they may turn out to be particularly useful in the treatment of heart failure (Berger et al., 2001) and renal disease (Benigni, 2000). Whether they will be useful for hypertension and other vascular diseases remains to be seen (Lüscher and Barton, 2000).

Other Vasoconstrictors

Prostaglandin H_2 and thromboxane A_2 are among other possibly important constricting factors (Ungvari and Koller, 2000).

ARTERIAL STIFFNESS: BASIC PRINCIPLES

In concert with the various functional and structural changes that are responsible for hypertension, the arteries become stiffer or less compliant. Vascular stiffness progressively increases with age (Slotwiner et al., 2001) and is responsible for the progressive increase in systolic as compared to diastolic pressure, leading to the typical widening of pulse pressure that is now recognized to be the major determinant of cardiovascular risk, as described in Chapter 1 (Beltran et al., 2001).

With increasing recognition of the importance of arterial stiffness, increasing attention is being directed to various indices of the properties of arteries that can be measured, as listed in Table 3-7. Such measures of stiffness and compliance are being shown to be an independent predictor of the development of hypertension (Liao et al., 1999) and a marker of cardiovascular risk in those with hypertension (Blacher et al., 1999).

Elastic modulus	Pressure step required for (theoretic) 100% stretch from resting diameter at fixed vessel length
Arterial distensibility	Relative diameter (or area) change for a pressure increment; the inverse of elastic modulus
Arterial compliance	Absolute diameter (or area) change for a given pressure step at fixed vessel length
Volume elastic modulus	Pressure step required for (theoretic) 100% increase in volume
Young's modulus	Elastic modulus per unit area; the pressure step per cm^2 required for (theoretic) 100% stretch from resting length
Pulse-wave velocity	Speed of travel of the pulse along an arterial segment
Characteristic impedance	Relationship between pressure change and flow velocity in the absence of wave reflections
Stiffness index	Ratio of logarithm [systolic-diastolic pressures] to relative change in diameter

Modified from O'Rourke M. Mechanical principles in arterial disease. Hypertension 1995;26:2–9.

TABLE 3-7. *Indices of arterial stiffness*

Different impacts of these various measures have been noted. For instance, arterial stiffness measured by the pressure-independent stiffness index was associated with aging and left ventricular remodeling but not hypertrophy, whereas BP and the elastic modulus were associated with left ventricular hypertrophy (Roman et al., 2000). Changes in compliance identified by pressure pulse contour analysis were independent of changes in BP with age (McVeigh et al., 1999).

The large arteries act as conduits and cushions, the first to deliver blood with a minimal fall in pressure to peripheral tissues, the second to smooth out “the pulsations imposed by the intermittently contracting heart so that blood is directed through these tissues in an almost steady stream” (O'Rourke, 1995).

Changes in the physical characteristics of the large arteries reflected in the BP pulse contour alter not only BP and pulse pressure but also cardiac work and performance. A reduction in arterial compliance increases systolic BP but lowers diastolic BP. With rigidity of the aorta and capacitance arteries, peripheral runoff of the stroke volume will be greater during systole; with impaired elastic recoil of the aorta, less buffering of the fall in BP will occur, lowering diastolic BP even further, as schematized in Figure 3-28.

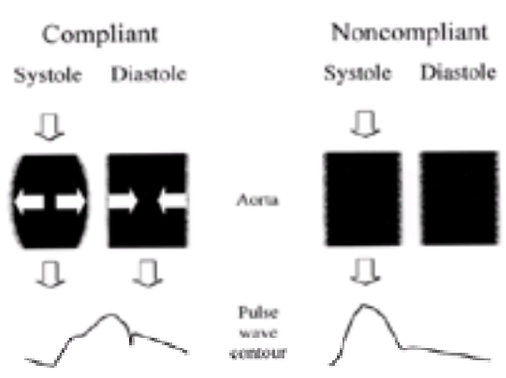

FIG. 3-28. The compliant aorta expands during systole and recoils during diastole, whereas there is little change in the noncompliant vessel, raising the systolic blood pressure and lowering diastolic blood pressure. The change in the pulse-wave contour reflects the augmentation of systolic pressure caused by the more rapid wave reflection back from the periphery. (Modified from Glasser SP. On arterial physiology, pathophysiology of vascular compliance, and cardiovascular disease. *Heart Dis* 2000;2:375–379.)

The progressive reduction in large-artery compliance changes the pulse-wave contour and adds to cardiac work. As stated by McVeigh et al. (2001):

> [In youth] the optimal coupling between the left ventricle and the arterial system results in a characteristic pressure pulse contour where wave reflection from high impedance resistance vessels produces a readily apparent secondary pressure rise in late diastole that serves to augment coronary perfusion. With a reduction in large artery compliance, the forward pressure wave travels with an increased velocity and is reflected from the high impedance resistance vessels arriving back at the heart prematurely producing a secondary systolic pressure peak

that can augment the systolic blood pressure [Fig. 3-28]. . . . The pathophysiologic consequence of these changes is a higher left ventricular impedance load and lower coronary perfusion pressure.

CELL MEMBRANE ALTERATIONS

The preceding sections reviewed the possible role of various factors acting through presumably normal cell membranes. There is, however, a body of evidence that shows that the cell membranes of hypertensive animals and, less convincingly, of hypertensive people are altered in a primary manner, allowing abnormal movement of ions and thereby changing the intracellular environment to favor contraction and growth (Swales, 1990a) (Fig. 3-29). These primary alterations are differentiated from the secondary inhibition of the Na^+/K^+-ATPase pump by a putative natriuretic hormone secreted after volume expansion, described earlier in this chapter, that may be a mechanism for renal sodium retention.

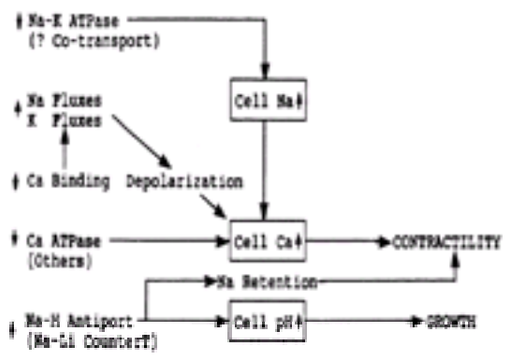

FIG. 3-29. Hypotheses linking abnormal ionic fluxes to increased peripheral resistance through increases in cell sodium (Na), calcium (Ca), or pH. ATPase, adenosine triphosphatase; CounterT, countertransport; K, potassium; Li, lithium. [Reprinted from Swales JD. Functional disturbance of the cell membrane in hypertension. J Hypertens 1990a;8(Suppl 7):S203–S211, with permission.]

Ion Transport across Membranes

Figure 3-30 portrays some of the transport systems present in the cell membrane of erythrocytes that control the movement of sodium and potassium to maintain the marked differences in concentration of these ions on the outside and inside of cells, differences which, in turn, provide the electrochemical gradients needed for various cell functions (Jackson, 2000). Abnormalities of the physical properties of the membrane and of multiple transport systems have been implicated in the pathogenesis of hypertension (Russo et al., 1997). Most of what follows relates to vascular smooth muscle cells but, because such cells are not available for study in humans, surrogates such as red and white blood cells have been used. There are serious reservations about the pertinence of these *in vitro* measurements to *in vivo* changes (Swales, 1991), but at least some of these *in vitro* findings have also been seen in vascular smooth muscle cells of hypertensive rats and humans (Orlov et al., 1999).

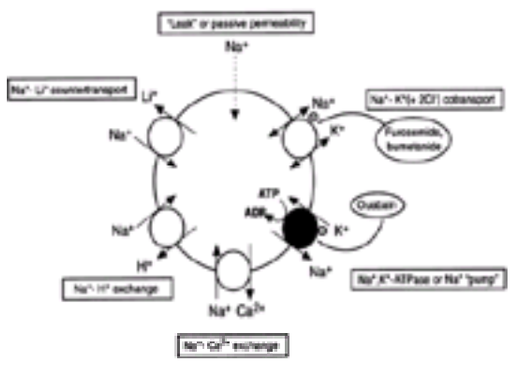

FIG. 3-30. Abnormalities of one or more of the sodium (Na^+) transport pathways depicted are thought to contribute to the development of essential hypertension. Solid circle, active transport; open circles, passive transport; open ovals, inhibitors. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Ca^{2+}, calcium; Cl^-, chlorine; H^+, hydrogen; K^+, potassium; Li^+, lithium. (Reprinted from Weder AB. Membrane sodium transport. In: Izzo JL, Black HR, Taubert TA, eds. *Hypertension primer*, 2nd ed. Dallas: American Heart Association, 1999;52, with permission.)

With the tremendous amount of research in this area over the last 30 years, it has become obvious that none of these defects is present in all or even the majority of hypertensives, and Swales in particular questioned their pathogenetic role. He concluded that “the best unifying hypothesis is that all the reported abnormalities are markers for a disturbance of physicochemical properties of the cell membrane lipids of hypertensive patients” (Swales, 1990b). Because the active transport of sodium is a fundamental property of all cells, even minor changes in the properties of cell membranes could lead to secondary alterations in sodium transport (Swales, 1991).

Intracellular Sodium

Most measurements of intracellular sodium have found higher concentrations in cells from hypertensives than in those from normotensives (Lijnen, 1995). However, a number of technical, environmental, and racial factors have been recognized to affect red blood cell sodium concentration. For example, a low-sodium diet will reduce the concentration, likely as a consequence of increased activity of the Na^+/K^+-ATPase pump (Lijnen et al., 1986).

Sodium-Hydrogen Exchange

The sodium-hydrogen exchange antiporter, by exchanging intracellular H^+ for extracellular Na^+, is essential for multiple cell functions, including regulation of pH, volume, and growth. Aviv (1996) has provided evidence that the exchanger is stimulated in some hypertensive patients either by an increased cellular calcium load or by enhanced external calcium entry.

An increased Na^+/H^+ exchanger could play a significant role in the pathogenesis of hypertension, both by stimulating vascular tone and cell growth and, possibly, by increasing sodium reabsorption in renal proximal tubule cells (Soleimani and Singh, 1995). In 12 of 27 hypertensives, high Na^+/H^+ exchanger activity was associated with lower fractional sodium excretion and inappropriately low levels of plasma renin activity (Díez et al., 1995).

Sodium-Lithium Countertransport

To simplify measurements without using radioisotopes, under appropriate conditions intracellular H^+ can be replaced by Li^+, and the exchange for external Na^+ can be measured as sodium-lithium countertransport (SLC) (Canessa, 1995). SLC is under genetic control and is increased in many hypertensives and patients with diabetic nephropathy. Whatever its role, SLC has been noted to be the most frequent and persistent measure of abnormal red blood cell sodium transport in hypertensives (Turner and Sing, 1996). Over 6- to 8-year follow-up periods, high SLC was significantly associated with the incidence of hypertension (Laurenzi et al., 1997; Strazzullo et al., 1998).

Alterations in Cell Membranes

Red blood cell membranes from hypertensives have an increased cholesterol-phospholipid ratio in association with high SLC (Villar et al., 1996) and increased ratios of fatty acid metabolites to precursors as compared to those from age-matched normotensives (Russo et al., 1997). Such changes in lipids produce a high membrane microviscosity and decrease in fluidity (Carr et al., 1995), which may be responsible for increased permeability to sodium and other alterations in sodium transport (Dominiczak et al., 1994). As summarized by Zicha et al. (1999): "Lipid-dependent modifications in cells participating in cardiovascular regulation might be a part of pathogenic mechanisms responsible for chronic blood pressure elevation."

Calcium Transport and Binding

Even mild mechanical perturbation of cultured endothelial cells causes a rapid increase of intracellular calcium (Sigurdson et al., 1993). It is easy to visualize a major contribution of increased membrane calcium concentrations to the heightened vascular tone that is involved in the increased PR of hypertension. A significantly increased calcium content was found in the membranes of red blood cells in 39 untreated hypertensives as compared to 40 normotensives (Kosch et al., 2001). Both plasma and intracellular calcium concentrations were similar in the two groups. Even without increases in calcium concentration, vasoactive stimuli may act through calcium signaling. In some manner, two endothelium-derived vasoconstrictors, endothelin and thromboxane A_2, increased the calcium sensitivity of the contractile apparatus of arteriolar smooth muscle so that similar increases in intracellular calcium elicited greater myogenic constriction (Ungvari and Koller, 2000).

Ion Channels

The functions of ion channels across cell membranes are fundamental determinants of vascular tone (Jackson, 2000). However, other than their involvement in some of the rare monogenic forms of hypertension noted earlier in this chapter, there is little evidence that dysfunction of these channels plays a role in human hypertension.

Now that various mechanisms that may induce hypertension either through CO or PR have been covered, consideration may be given to some other factors that may be either causal or coincidentally connected to hypertension.

OBESITY-RELATED HYPERTENSION

The majority of people in the United States are overweight [defined as a body mass index (BMI) above 25], and more than 20% are obese (defined as a BMI ³30) (National Task Force, 2000). Increasing obesity is common to all developed societies (Jacobsen et al., 2001) and has been seen particularly among children (Chinn and Rona, 2001). Perhaps most ominous is the striking increase in abdominal or visceral obesity, known to be associated with worse metabolic consequences, including diabetes and dyslipidemia, than more generalized obesity (Montague and O'Rahilly, 2000). As seen in Figure 3-31, 80% of U.S. black and Hispanic women and 60% of white women older than 50 have abdominal obesity (Okosun et al., 1999).

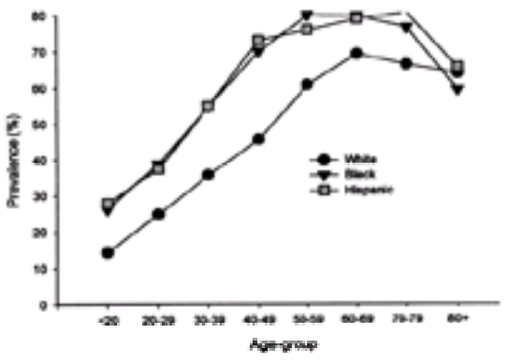

FIG. 3-31. Age-specific prevalence of abdominal obesity in U.S. women from the National Health and Nutrition Examination Survey III. Abdominal obesity is defined as a waist circumference greater than 88 cm or 34 in. (Modified from Okusun IS, Prewitt TE, Cooper RS. Abdominal obesity in the United States: prevalence and attributable risk of hypertension. *J Hum Hyper-tens* 1999;13:425–430.)

Association with Hypertension

Weight gain, even to levels not considered to be a problem, increases the incidence of hypertension. This was clearly shown in a cohort study of more than 80,000 women participating in the Nurses' Health Study (Huang et al., 1998) (Fig. 3-32). Those women, now in midlife, who had gained as little as 5 kg over their weight at age 18 had a 60% higher relative risk of developing hypertension than did those whose weight had not changed more than 2 kg. Those who gained 10 kg or more had a 2.2-fold greater risk. Similar increases have been observed in other populations (Wilsgaard et al., 2000), and even children who gain weight have a rise in BP (He et al., 2000). A further estimate of the association comes from the Framingham Study: Seventy percent of hypertension in men and 61% in women were directly attributable to excess adiposity; a 4.5–mm Hg average increase in systolic BP was seen with every 10-pound weight gain (Kannel et al., 1993).

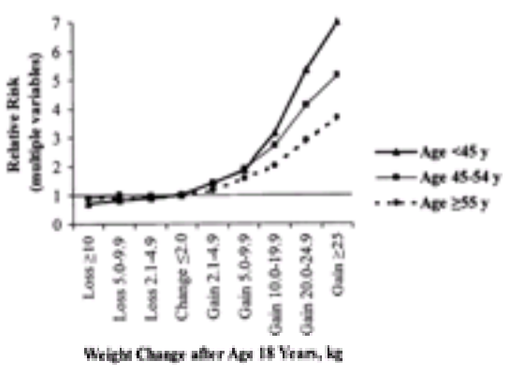

FIG. 3-32. Multivariate relative risk for hypertension according to weight change after 18 years within strata of age among U.S. women enrolled in the Nurses' Health Study. Adjusted for age, body mass, index at age 18 years, height, family history of myocardial infarction, parity, oral contraceptive use, menopausal status, post-menopausal use of hormones, and smoking status. (Modified from Huang Z, Willett WC, Manson JE, et al. Body weight, weight change, and risk of hypertension in women. *Ann Intern Med* 1998;128:81–88.)

Mechanisms of Hypertension with Obesity

Hemodynamics

CO, stroke volume, and intravascular volume are increased in obese hypertensives, with an even closer correlation to fat-free body mass than to adipose mass (Collis et al., 2001). With weight loss, stroke volume and CO go down along with the BP (Stevens et al., 2001).

Hormonal Factors

A number of hormonal factors have been implicated in obesity-related hypertension, including an increased level of SNS activity (Grassi et al., 2000) that may reflect a failure to suppress cardiac sympathetic outflow (Rumantir et al., 1999). Increased renin-angiotensin activity may arise from adipose tissue itself (Engeli et al., 2000). Obese people, normotensive or hypertensive, have diminished nitric oxide mediated vasodilation (Higashi et al., 2001).

Insulin Resistance and Hyperinsulinemia

The increased number of adipocytes in obese people secrete a number of substances that may engender insulin resistance, including free fatty acids (Bergman et al., 2001), and multiple polypeptides, including the recently identified hormone resistin (Steppan et al., 2001). The majority of obese people are insulin-resistant. The resultant hyperinsulinemia that attempts to maintain normoglycemia may be overwhelmed, and type 2 diabetes supervenes. Increases in free fatty acids have multiple deleterious effects, including a decrease in insulin sensitivity by inhibiting glucose transport in muscles (Shulman, 1999) and impairing insulin-mediated vasodilation and NO production (Balletshofer et al., 2000). As seen in Figure 3-33, hypertension may develop from various effects of hyperinsulinemia per se or from the insulin resistance itself. These various features have been called *syndrome X* (Reaven, 1988) but are better known as the*metabolic syndrome*.

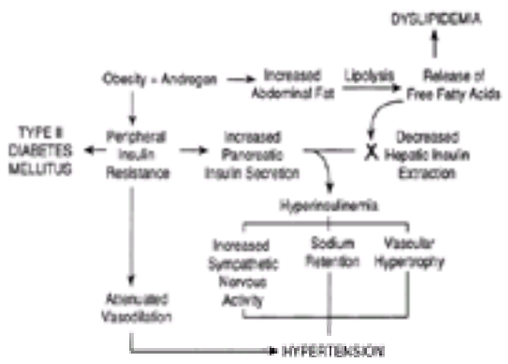

FIG. 3-33. Overall scheme for mechanisms by which obesity, if particularly predominantly upper body or visceral in location, could promote diabetes, dyslipidemia, and hypertension via hyperinsulinemia.

Sympathetic Activation

Obesity-induced hypertension has been shown to arise from the interactions of at least four mechanisms (Fig. 3-33). Increased sympathetic activity may arise not only from obesity-induced hyperinsulinemia but also from a direct effect of increased caloric intake (Landsberg, 2001). Higher rates of muscle sympathetic nerve activity are found in obese subjects (Scherrer et al., 1994), whether or not they are hypertensive (Gudbjörnsdóttir et al., 1996). Chronic hyperinsulinemia was found to be associated with a high-output, low-resistance hemodynamic state, persistent baroreflex downregulation, and postprandial sympathetic dominance, all of which were reversed by weight loss (Emdin et al., 2001). As will be noted, insulin normally induces vasodilation in skeletal muscle but, in obese patients, little or no increase in muscle blood flow occurs in response to insulin (Vollenweider et al., 1994), perhaps because of an augmented pressor sensitivity to norepinephrine (Baron et al., 1994).

Renal Effects

As shown in multiple models, insulin increases renal sodium reabsorption (Gupta et al., 1992). At the same time, obese individuals, whether or not they are hypertensive, tend to have higher rates of glomerular filtration and renal plasma flow that are correlated with fasting insulin levels (Ribstein et al., 1995). The hyperfiltration and perfusion also were associated with more albuminuria, posing the threat of greater renal damage in obese hypertensives.

Impaired Vasodilation

The last of the possible mechanisms for hypertension with obesity is an impaired ability of insulin to dilate the peripheral vasculature as it does in nonobese young people (Laakso et al., 1990). Insulin infused into healthy subjects stimulates both endothelin-1 and NO activity (Cardillo et al., 1999). In hypertensives, reduced insulin-mediated vasodilation is associated with reduced endothelial NO production (Cleland et al., 2000).

As attractive as the scheme shown in Figure 3-33 may appear, the role of insulin resistance and hyperinsulinemia in obesity-related hyper-tension has been questioned. In particular, John Hall and colleagues (2001) have provided experimental evidence that there is no direct cause-and-effect relationship between insulin and hypertension, suggesting that the associations between hyperinsulinemia and hypertension occur through parallel but unlinked mechanisms that are not related primarily to the effects of obesity per se. Support for this parallel but unconnected relation has also come from comparisons in sib-ling pairs, in whom very little of BP variance has been explained by insulin levels after adjustment for BMI (Kronenberg et al., 2000).

Leptin

Recently, a possible role for leptin, the hormone produced mainly in fat cells, has been postulated (Hall et al., 2001). Higher circulating leptin levels have been found in hypertensives (Henriksen et al., 2000), particularly in those who are insulin resistant (Galderisi et al., 2001), but the relationship between leptin and BP has, in general, not been very close (Stenvinkel, 2000). As Stenvinkel (2000) notes:

> Leptin has several effects, such as stimulation of the renin-angiotensin and sympathetic nervous system. . . . On the other hand, leptin also stimulates natriuresis, so it is possible that a blunted effect of leptin, i.e. peripheral leptin resistance, may predispose to hypertension. . . . If patients with hyperleptinemia are resistant to the facilitative effects of leptin on sodium excretion, but are not resistant to the stimulatory effects of leptin on sympathetic and/or renin-angiotensin activity, this would explain why hypertension occurs so often in obesity.

With weight gain, both hyperinsulinemia and hyperleptinemia were noted, but both were thought to be only ancillary to stimulation of SNS activity (Masuo et al., 2000). Furthermore, in a twist of usual thinking, Julius et al. (2000) have hypothesized that a primary increase in sympathetic tone may be responsible for both hypertension and weight gain, the latter from a downregulation of b-adrenergic receptors that normally increase energy expenditure. Thereby, hypertensives would tend to gain weight and have great difficulty in losing weight.

Obviously, the mechanisms by which obesity induces hypertension are multiple and uncertain. As seen in Figure 3-34, Hall (2000) has put together another scheme deleting hyperinsulinemia and adding a direct effect of increased renal interstitial hydrostatic pressure from increased amounts of locally produced hyaluronan (Dwyer et al., 2000), leaving leptin only as a contributor to sympathetic overactivity. What is shown to lead to both hypertension and renal damage may be only part of the story: Adipose tissue is a veritable factory for vasoactive substances (Ahima and Flier, 2000), many of which may affect BP.

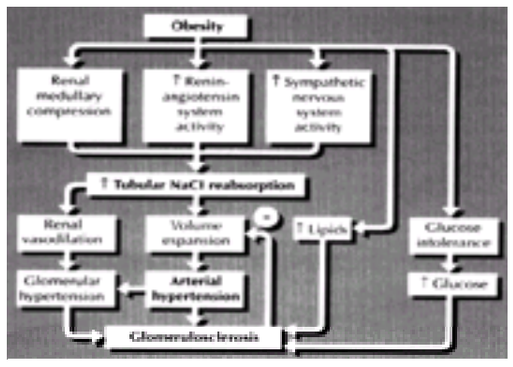

FIG. 3-34. Mechanisms by which obesity may cause hypertension and renal injury by activation of the renin-angiotensin system and sympathetic nervous system, metabolic abnormalities, and compression of the kidney. NaCl, sodium chloride. (Reprinted from Hall JE. Pathophysiology of obesity hypertension. *Curr Hypertens Rep* 2000;2:139–147, with per-mission.)

INSULIN RESISTANCE WITHOUT OBESITY

As we have seen, insulin resistance and resultant hyperinsulinemia are common in obesity and may play a role in obesity-related hypertension. However, an association between insulin resistance and hypertension has also been seen in nonobese hypertensives (Reaven et al., 1996). These persons have been referred to as “metabolically obese, normal-weight” individuals (Ruderman et al., 1998).

Observations on the Relation between Insulin Resistance and Hyperinsulinemia

Using the euglycemic hyperinsulinemic clamp procedure to assess insulin sensitivity, Lind et al. (1995) found that 31% of 420 untreated middle-aged hypertensives had insulin resistance. One-half of these insulin-resistant hypertensives had abdominal obesity, and one-half had dyslipidemia. If those with abdominal obesity are excluded, the prevalence of insulin resistance in presumably nonobese hypertension falls to 15%.

Although hyperinsulinemia has been found to precede the development of hypertension in nonobese people (Salonen et al., 1998), most of the association is seen in those with other evidence of the metabolic syndrome, particularly dyslipidemia. In some studies, hypertension per se is not associated with insulin resistance, whereas even small increments of body fat bring out the impairment in insulin sensitivity (Toft et al., 1998). Ruderman et al. (1998) conclude, “In most, though not all, studies in which nonobese individuals with 'metabolic obesity, normal weight' were identified, they had a slightly higher BMI or a greater calculated fat mass than did the control subjects.”

Assuming that insulin resistance does presage and accompany hypertension in at least some truly nonobese people, most of the positive associations have been found in whites. Other ethnic groups apparently do not display the association between hyperinsulinemia or insulin resistance and hypertension found in white subjects. Although marked insulin resistance has been found in Pima Indians (Saad et al., 1991) and Mexican-Americans (Haffner et al., 1996), these two groups do not have an increased prevalence of hypertension. No differences in plasma insulin levels were found between normotensive and hypertensive Micronesian, Polynesian, and Melanesian populations (Dowse et al., 1993) or blacks on the island of Seychelles (Tappy et al., 1991).

The fact that certain ethnic groups may not have the association of hypertension and insulin resistance most likely means that genetic mechanisms and, possibly, environmental factors must also play a role and that they may override the influence of insulin (Reaven, 1993). Taken together, the data support a role for insulin resistance and hyperinsulinemia, but it is a role that is influenced strongly by environmental factors (e.g., genetics and the presence of obesity). Not all who are insulin-resistant are hypertensive, and the majority of nonobese hypertensives are not insulin-resistant. However, the two go together more often than would be expected by chance, and there are known mechanisms for their interaction.

Mechanisms for Insulin Resistance

As shown in Figure 3-33 and described previously, the manner by which obesity, particularly when predominantly abdominal, evokes hyperinsulinemia seems easy to explain. The explanation for the insulin resistance found in some nonobese hypertensives, however, is not obvious and may involve one or more aspects of insulin's action listed in Table 3-8.

Aspect	Normal site of action	Effect of hypertension
Insulin delivery	Capillary bed	Vasoconstriction; attenuated vasodilation; capillary rarefaction
Insulin transport	Interstitium	Impaired transport
Insulin action	Muscle fiber	Genetic or acquired increase in type 2B fibers; hormonal interference with insulin effects; decreased glucose transporter protein

TABLE 3-8. *Factors that may induce insulin resistance in hypertension*

- Delivery may be reduced by diminished blood flow, as seen acutely with sympathetic activation (Jamerson et al., 1993) or chronically from failure of capillary recruitment (Baron et al., 2000). Moreover, the insulin-mediated vasodilative action that normally increases muscle blood flow is attenuated in patients with hypertension (Laine et al., 1998).
- Transport, shown to be rate-limiting for insulin action (Yang et al., 1989), may be reduced by changes in cell membranes.
- The action of insulin within skeletal muscle may be impaired for multiple reasons. Of these, an inherited or acquired predominance of type 2B (white) muscle fibers—which are more resistant to the effects of insulin than are types 1 and 2A (red) fibers (James et al., 1985)—has been demonstrated (Juhlin-Dannfelt et al., 1979) and shown to be associated with *in vivo* insulin resistance (Mårin et al., 1994).

As will be noted, most of these abnormalities may reflect the effects of physical inactivity (Endre et al., 1994; (Julius et al., 1991a).

Mechanisms for Hypertension

However they occur, insulin resistance and hyperinsulinemia may lead to hypertension by the multiple pathways shown in Figure 3-33. Of these, impaired endothelium-dependent vasodilation may be particularly important (Baron, 1996). Insulin normally acts as a vasodilator (Anderson and Mark, 1993; Baron et al., 1993). As seen in Figure 3-35, Anderson and Mark (1993) have shown that although insulin increases sympathetic noradrenergic activity to skeletal muscle, the effect is normally overridden by the direct vasodilative effect of insulin. However, patients with hypertension (Baron et al., 1993) and healthy elderly subjects (Hausberg et al., 1997) have a defect in this vasodilative action and fail to increase muscle blood flow in response to insulin infusions. In combination with high levels of sympathetic nervous activation (described earlier in this chapter), the effects of attenuated vasodilation could enable insulin to raise the BP in patients who are obese or hypertensive (Fig. 3-35).

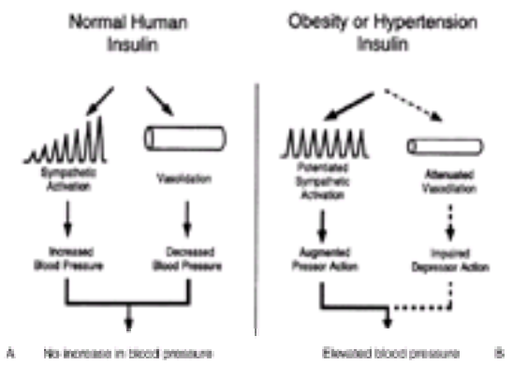

FIG. 3-35. A: This panel represents insulin's actions in normal humans. Although insulin causes marked increases in sympathetic neural outflow, which would be expected to increase blood pressure, it also causes vasodilation, which would decrease blood pressure. The net effect of these two opposing influences is no change or a slight decrease in blood pressure. There may be an imbalance between the sympathetic and vascular actions of insulin in conditions such as obesity and hypertension. **B:** Insulin may cause potentiated sympathetic activation or attenuated vasodilation. An imbalance between these pressor and depressor actions of insulin may result in elevated blood pressure. (Reprinted from Anderson EA, Mark AL. Cardiovascular and sympathetic actions of insulin. *Cardiovasc Risk Factors* 1993;3:159–163, with permission.)

Thus, there are differences between the relatively short-term effects of insulin in normal people and the long-term effects of hyperinsulinemia in patients who are genetically or otherwise predisposed to express prohypertensive effects. Such differences may also explain the absence of hypertension in patients with hyperinsulinemia from insulinomas (O'Brien et al., 1993) or with the polycystic ovary syndrome (Zimmermann et al., 1992).

Additional evidence in favor of a hypertension-inducing effect of hyperinsulinemia is the lowering of BP by the use of agents such as glitazones that increase insulin sensitivity and lower insulin levels (Matthaei et al., 2000).

Role of Physical Inactivity

A relatively simple and straightforward mechanism may explain much of the association between insulin resistance and hypertension, an association that also commonly is seen with any degree of obesity: physical inactivity. As an example, Fossum et al. (1999) found a close correlation between insulin sensitivity and physical fitness in a group of young hypertensives. Blair and colleagues have repeatedly shown an association between reduced physical fitness and the development of both hypertension (Blair et al., 1984) and type 2 diabetes (M Wei et al., 1999).

As Ruderman et al. (1998) summarize in their analysis of the “metabolically obese, normal-weight” situation:

> The interrelationships between insulin resistance, inactivity, and poor aerobic fitness appear to be quite strong, even in normal-weight individuals. The finding of a decreased VO_{2max} in young patients before the development of disorders associated with the insulin resistance syndrome raises the interesting possibility that decreased fitness and/or physical activity are important factors in their development. It is unclear to what extent central obesity, which often accompanies decreased fitness, contributes to the association between inactivity and insulin resistance. Regular exercise ameliorates the entire cluster of metabolic and hemostatic abnormalities found in patients with insulin resistance. In addition, it tends to reverse the abnormal body composition and fat distribution found in these individuals. A reasonable hypothesis is that the apparent effectiveness of regular exercise in decreasing the incidence of coronary heart disease and type 2 diabetes is due to its effects on insulin action and central adiposity. If so, interventions to increase levels of physical activity, particularly in children, adolescents, and young adults, may be an effective approach to prevent or retard the development of the increasing number of disorders associated with insulin resistance.

The bottom line comes back to the need for prevention; increased levels of physical activity may be the most effective preventive measure.

DIABETES AND HYPERTENSION

The current epidemic of type 2 diabetes occur-ring in all developed societies is a reflection of the interactions among obesity, physical activity, and insulin resistance described in the two pre-ceding sections. The problem is being seen even in children, because they are becoming increasingly obese (Fagot-Campagna et al., 2001).

Prevalence

Diabetes mellitus and hypertension coexist more commonly than is predicted by chance, perhaps three times more commonly. In those with insulin-dependent diabetes (type 1), hypertension is seen in most of the 40% who develop nephropathy but is seen no more frequently in those who escape nephropathy than in the nondiabetic population (Nørgaard et al., 1993). In those with insulin-independent diabetes (type 2), almost all of whom are obese, hypertension is more common than among obese people without diabetes (Hypertension in Diabetes Study Group, 1993). As noted earlier, the connection between hyper-tension, diabetes, and obesity is even stronger in those whose obesity is predominantly in the upper body, comprising the major components of the metabolic syndrome.

Mechanisms

In both type 1 and type 2 diabetics, hyperinsulinemia is present: in type 1, because the amount of exogenous insulin given is larger than the normal endogenous levels; in type 2, because of obesity-induced insulin resistance with resultant increased secretion of insulin in the eventually futile attempt to maintain euglycemia.

The hypertension seen in type 2 diabetics is characterized by both volume expansion and increased vascular resistance, the latter related to the accelerated atherosclerosis that is common with long-standing hyperglycemia. Hyperglycemia per se inhibits endothelium-derived relaxation (Williams et al., 1998) and stimulates transcription of the genes for growth factors acting on vascular smooth muscle cells (McClain et al., 1992).

The consequences of the coexistence of diabetes and hypertension are covered in Chapter 4 and the treatment of the diabetic hypertensive in Chapter 7. The special problems of diabetic nephropathy are described in Chapter 9.

OTHER POSSIBLE MECHANISMS FOR PRIMARY HYPERTENSION

The preceding exposition of the multiple factors shown in Figure 3-3 does not, unfortunately, exhaust the possible mechanisms for primary hypertension. The evidence for the mechanisms that follow is less impressive, and some of these factors seem to affect only a portion of the larger hypertensive population.

Abnormal Steroid Metabolism

In addition to the known monogenic forms of hypertension involving mineralocorticoid effects shown in Figure 3-1 and described in Chapter 13 and Chapter 14, claims have been made for a number of abnormal patterns of adrenocortical response to stimulation and types of hormones secreted. Increased levels of urinary free cortisol have been found in sodium-resistant hypertensives (Litchfield et al., 1998), and a relation has been shown between cortisol and left ventricular mass independent of BP (Duprez et al., 1999). Slightly elevated corticosterone levels (Soro et al., 1996) and increased vasoconstrictor sensitivity to glucocorticoids (Walker et al., 1996) have also been reported.

Vasoactive Peptides

In addition to the more probable involvement of AII and endothelin, a less probable and still not completely worked out role has been claimed for a large number of other vasoactive peptides, including a large number of growth factors (Fig. 3-26).

Natriuretic Peptide Family

The discovery by deBold et al. (1981) of a rapid natriuretic effect of injection of atrial extract (i.e., atrial natriuretic peptide) has been followed by the identification of a family of natriuretic peptides (Wilkins et al., 1997). The family includes two additional peptides that share both structure and function with the atrial peptide—brain and C-type. These peptides are entirely unlike the ouabainlike natriuretic factor described earlier.

The natriuretic peptides respond to an increase in intravascular volume, acting primarily on the kidney to increase sodium excretion, on the vasculature to induce vasodilation, and on the adrenal glands to reduce aldosterone secretion, effects that counter the major effects of the renin-aldosterone mechanism. However, there is no convincing evidence for a role of the natriuretic family in the pathogenesis or course of hypertension (Talwar et al., 2000). They may be valuable as markers of heart failure (Cheng V et al., 2001) and may prove useful in treatment of decompensated congestive heart failure (Colucci et al., 2000). Moreover, orally effective neutral endopeptidase 24.11 inhibitors, which prevent the breakdown of various endogenous peptides including the natriuretic family, may prove useful in the treatment of hypertension and other cardiovascular diseases.

Adrenomedullin

In 1993, Kitamura et al. described the isolation of a new hypotensive peptide from an extract of human pheochromocytoma tissue and then from normal adrenal medulla—adrenomedullin. Since then, considerable information about the synthesis and biology of adrenomedullin has been provided (Charles et al., 1999). When given in moderately large intravenous doses to hypertensives, this peptide lowered BP, increased CO, and stimulated the sympathetic and renin systems, but did not change urinary excretions (Troughton et al., 2000). Renal excretion is increased with elevated sodium intake and is closely linked to endothelin levels (Cuzzola et al., 2001).

Kallikrein and Bradykinin

The kallikrein-bradykinin system (Fig. 3-36) has long been recognized and has recently been the focus of considerable basic and clinical research. The renewed interest relates largely to increasing evidence that increased levels of bradykinin contribute to the beneficial effects of ACEIs (Reid et al., 2000) as well as to their most common side effect—cough (Mukae et al., 2000). Because the kininase that inactivates bradykinin is inhibited by ACEIs, the subsequent higher levels of bradykinin induce vasodilation by endothelium-dependent hyper-polarization (Honing et al., 2000) and involve increased prostacyclin synthesis (Yamasaki et al., 2000). The specific bradykinin B_2 receptor antagonist icatibant attenuates the fall in BP in response to an ACEI (Squire et al., 2000). Moreover, patients with primary hypertension may have impaired vasodilation in response to bradykinin (Taddei et al., 1999).

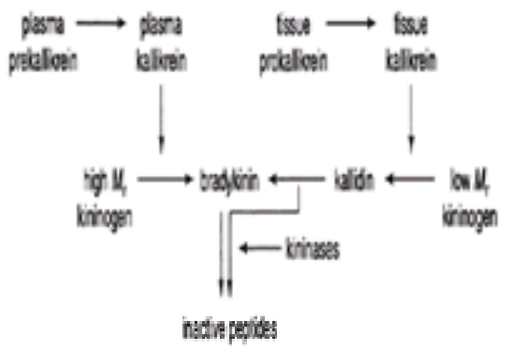

FIG. 3-36. Two kinin-release systems involving plasma kallikrein and tissue (glandular) kallikrein.

Whether contributing only to the benefits of ACEIs or providing additional benefits, including effects on insulin sensitivity and thrombogenesis (Fogari and Zoppi, 2000), bradykinin may play a greater role in human hypertension than was previously recognized.

For many years, urinary kallikrein excretion has been known to be reduced in blacks and in subjects with a family history of hypertension. The lower excretion in blacks is correlated with lower potassium excretion. Women, regardless of ethnicity, excrete kallikrein more than men (Song et al., 2000).

Other Vasoactive Peptides

Less is known about the role of a number of other vasoactive peptides in human hypertension. These include

- Adenosine (Ledent et al., 1997)
- Calcitonin gene–related peptide (Preibisz, 1993)
- Dopamine (Kuchel, 1999)
- Melatonin (Arangino et al., 1999)
- Neuropeptide Y (Michel and Rascher, 1995)
- Opioid peptides (McCubbin et al., 1998)
- Parathyroid hormone–related peptide (Schlüter and Piper, 1998)
- Serotonin (Missouris et al., 1998)
- Substance P (Newby et al., 1997)
- Vasopressin (Mohr and Richter, 1994).

Beyond these, various proinflammatory cytokines (Laviades et al., 2000; Peeters et al., 2001) and oxygen free radicals (Lacy et al., 2000) may be involved in the development of hypertension.

Prostaglandins

Various prostaglandins have different sites of origin and different effects on BP. Platelet-derived thromboxanes promote platelet aggregation, constrict vascular smooth muscle, and may inhibit sodium excretion. Prostacyclin, synthesized within the blood vessel wall, inhibits plate-let aggregation; relaxes vascular smooth muscle; and, by reducing renal vascular resistance, pro-motes natriuresis. Prostaglandin E_2 is vasodilative, and prostaglandin F_2a is vasoconstrictive. As autocrine or paracrine hormones, they may be involved in both contraction and relaxation of vascular smooth muscle (Fig. 3-27).

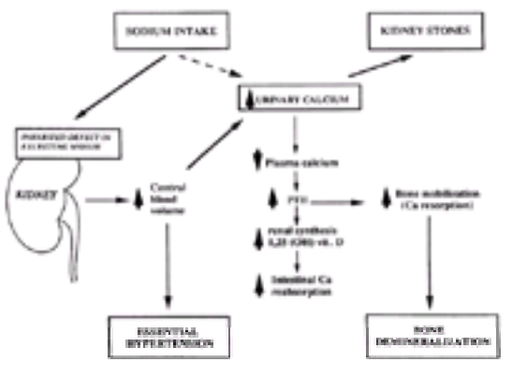

FIG. 3-37. Hypothesis on the possible link between the kidney, essential hypertension, and bone demineralization. 1,25 (OH) vit. D, 1,25-dihydroxyvitamin D; Ca, calcium; PTH, parathyroid hormone. (Reprinted from MacGregor GA, Cappuccio FP. The kidney and essential hypertension: a link to osteoporosis? J Hypertens 1993;11:781–785, with permission.)

Despite numerous findings that suggest a role for prostaglandins, the general impression is that prostaglandins probably are not major players in primary hypertension, although clearly they are important in circulatory control and thrombosis. Prostacyclin biosynthesis, assessed by urinary excretion of metabolites, was not correlated with BP, either treated or untreated (Ritter et al., 1996). As is noted in Chapter 11, there is some evidence for a role for prostaglandins in the pathogenesis of preeclampsia.

However, prostaglandins may be needed to sustain the renal circulation in the face of any situation in which it is threatened (Imig, 2000). The inhibition of renal prostaglandins may be responsible for the slight rise in BP and the more impressive inhibition of the action of various antihypertensive agents with the use of nonsteroidal antiinflammatory drugs (Whelton, 2001).

Medullipin: The Renomedullary Vasodepressor Lipid

After 40 years of persistent work, Muirhead (1993) and co-workers documented both the existence and the role of a substance secreted from renal medullary cells that appears to function as a counterbalance to the effects of AII. The renomedullary hormone, called *medullipin I*, requires activation by the cytochrome P-450–dependent enzyme system of the liver into medullipin II.

The structure of this substance remains unknown, but its existence has been strongly inferred from multiple experiments in animals, wherein a rise in renal perfusion causes BP to fall (Göthberg, 1994). This hypotensive response depends on an intact renal medulla and is not altered by renal denervation or the inhibition of RAS or autonomic nervous function (Cowley, 1994). A patient with persistent hypotension associated with elevated medullipin levels has been described (Muirhead et al., 1993). Whether medullipin functions under normal circumstances and is involved in various human hypertensive diseases remains to be discovered.

CONTRIBUTING FACTORS

A number of secondary features may contribute to the role of the primary mechanisms of hyper-tension covered earlier in this chapter—for example, the major impact of physical inactivity on obesity and diabetes. Beyond these primary and secondary mechanisms, a variety of factors may raise the BP in those who are exposed and susceptible to them. Either because they do not impact the majority of individuals who develop hypertension or because they have only a minimal effect, these factors are considered to be contributing rather than causal. Most of modern society's major lifestyle faults can be included among the contributors: smoking, alcohol abuse, stress, physical inactivity, excessive caloric intake that causes obesity and dyslipidemia, and reduced intake of fresh fruits and vegetables (Hajjar et al., 2001). Some of these are more likely directly implicated, and they have been given more emphasis earlier in this chapter, including stress with sympathetic over-activity, obesity with insulin resistance, diabetes, and dyslipidemia.

Fetal Environment

As noted earlier in the section Reduced Nephron Number, the development of hypertension may begin *in utero*: Low birth weight, from intrauterine growth retardation, is associated with the subsequent development of hypertension in most surveys (Law and Shiell, 1996) (Fig. 3-16).

Calcium and Parathyroid Hormone

Beyond the probability that increased intracellular calcium is involved in the pathogenesis of hypertension, as noted earlier in this chapter, there are other aspects of the relationship between calcium and hypertension.

The following findings usually are noted in uncomplicated, untreated primary hypertension:

- Lower dietary intake of calcium (McCarron et al., 1984), particularly in people who drink alcohol daily (Dwyer et al., 1996).
- Increased urinary calcium excretion (McCarron et al., 1980), which is likely the reason for an increased incidence of kidney stones (Borghi et al., 1999) and perhaps, eventually, for lesser bone density (Cappuccio et al., 1999).
- Lower plasma ionized calcium levels (Hvarfner et al., 1990).
- Increased levels of parathyroid hormone in some, likely related to reduced intake of calcium (Jorde et al., 2000). Parathyroid hormone levels are even higher in blacks than whites (Fuleihan et al., 1994) and are potentially able to raise BP (Fliser et al., 1997).

One way to put the various components into a logical sequence is depicted in Figure 3-37 (MacGregor and Cappuccio, 1993). The starting point has long been known: Whenever intravascular volume is expanded and sodium excretion is increased, calcium excretion increases (Suki et al., 1968). Intake of more sodium leads directly to an increase in calcium excretion (Breslau et al., 1982). The remainder of the scheme fits with the known associations and strongly supports a reduction in dietary sodium intake rather than an increase in dietary calcium intake to help overcome the consequences.

Other Minerals

Potassium

Considerable data suggest that a lower intake of potassium is involved in hypertension (Tobian, 1988) and stroke mortality (Fang et al., 2000). These include population surveys showing an inverse relation between dietary potassium intake and BP (Hajjar et al., 2001; Stamler et al., 1997), particularly in blacks (Veterans Administration Cooperative Study Group, 1987) and extending to children (Geleijnse et al., 1990). Skeletal muscle potassium is decreased in untreated hypertensives (Ericsson, 1984). As noted in Chapter 6, potassium depletion will raise BP, whereas potassium supplementation may lower the BP. The overall potassium intake of modern people has certainly been reduced below that of our ancestors (Table 3-2), so there are logical reasons to advocate a return to a more “natural” higher-potassium–lower-sodium diet.

Magnesium

Magnesium, beyond its role in activation of many critical enzymes involved in intermediary metabolism and phosphorylation, works as a natural antagonist to many of the actions of calcium (Howard et al., 1995). Concentrations of serum and intracellular free magnesium are generally normal in hypertensives (Delva et al., 1996). An inverse relation between dietary magnesium intake and BP has been seen in large prospective population surveys (Ascherio et al., 1996; Stamler et al., 1997) but not in a cross-sectional survey (Hajjar et al., 2001). The effect of magnesium supplements is covered in Chapter 6.

Lead

Long-term exposure to even low levels of lead may lead to hypertension, perhaps by increased production of reactive oxygen species (Ding et al., 2001). Increased blood lead levels were associated with higher BPs among blacks examined in the third National Health and Nutrition Examination Survey (Vupputuri et al., 2000). Similarly, the presence of higher levels of lead in the patella has been associated with an increased risk of hypertension both in a sample of women in the Nurses' Health Study (Korrick et al., 1999) and in men in the Normative Aging Study (Cheng Y et al., 2001). These data fit with a 30-year follow-up of men in the Normative Aging Study, wherein low-level lead exposure was associated with renal impairment (Kim et al., 1996), as also was noted in Taiwan (Lin et al., 2001).

Other Trace Metals

More hypertension has been seen in association with long-term exposure to arsenic (Chen et al., 1995) and carbon disulfide (Egeland et al., 1992). In a 6-year follow-up of healthy children in Finland, no association was noted between BP and dietary, blood, or tissue levels of copper, zinc, or selenium (Taittonen et al., 1997). No association was found with exposure to environmental cadmium (Staessen et al., 2000).

Smoking

The nicotine in cigarette smoke acutely raises BP, even in addicted smokers (Groppelli et al., 1992) (Fig. 3-38). No tolerance develops, so the BP remains high as long as the patient continues to smoke (Verdecchia et al., 1995). However, the effect of each cigarette is transient and is over within 30 minutes; if the BP is taken in a smoke-free environment, as in most physicians' offices and clinics, the pressor effect may be missed. Cigars, if inhaled, and smokeless tobacco also raise BP (Bolinder and de Faire, 1998), but transdermal nicotine patches do not appear to do so (Khoury et al., 1996).

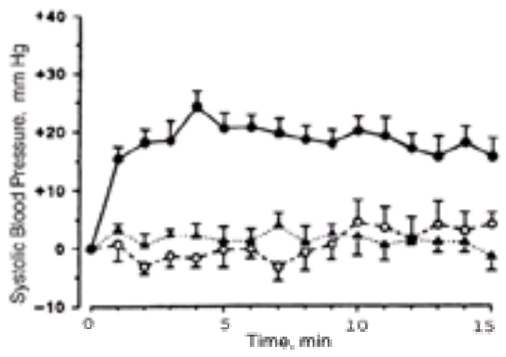

FIG. 3-38. Changes in systolic blood pressure over 15 minutes after smoking the first cigarette of the day: within the first 5 minutes (*solid circles*), during no activity (*open circles*), and during sham-smoking (*triangles*) in ten normotensive smokers. (Reprinted from Groppelli A, Giorgi DMA, Omboni S, et al. Blood pressure and heart rate response to repeated smoking before and after beta blockade and selective a $_1$ inhibition. *J Hypertens* 1992;10:495–499, with permission.)

Cross-sectional data on smokers and non-smokers are not consistent: Some studies find smokers to have a higher BP (Poulsen et al., 1998), whereas others find smokers to have a lower BP (Mikkelsen et al., 1997). However, there are inadequate data on repeated ambulatory BP monitoring of the same people while they are smoking or not smoking. Minami et al. (1999) found a 5/3–mm Hg lower daytime ambulatory BP 1 week after smoking cessation as compared to the BP while smoking. In contrast, progressive increases in BP were noted in men who quit smoking that could not be related to increases in body weight (Lee et al., 2001).

Regardless, all who smoke should be strongly advised to quit. Smoking is associated with insulin resistance (Rönnemaa et al., 1996), an attenuation of endothelium-dependent relaxation (Celermajer et al., 1996), and an increase in endothelin levels (Fernandez-Violante et al., 1996). These multiple adverse effects obviously add to the major cardiovascular damage induced by smoking (Bleyer et al., 2000).

Caffeine

Although considerable tolerance rapidly develops to the pressor effect of caffeine, the pressor response is regained after a few hours (Shi et al., 1993). Those who drink five cups or more of coffee per day have, on average, a 2.4/1.2–mm Hg higher BP than those who abstain (Jee et al., 1999). In a 32-year follow-up of 1,017 former medical students, the incidence of hypertension was nearly threefold higher in those who drank one to five cups of coffee per day as compared to non–coffee drinkers (Mead et al., 1996). In contrast, increasing caffeine intake, ascertained by multiple careful dietary recalls, was associated with *lower* BP among the participants in the Multiple Risk Factor Intervention Trial (Stamler et al., 1997).

Alcohol

The possible role of alcohol, in amounts consumed by a large part of the overall population, needs special emphasis. In contrast to its immediate vasodepressor effect (Kawano et al., 1996), chronic consumption, even of only moderate quantities, may raise the BP; in larger quantities, alcohol may be responsible for a significant amount of hypertension.

Nature of the Relationship

The association between alcohol and hypertension was reported in 1915 by Lian, but not until Klatsky et al. (1977) documented it in a large population was alcohol recognized as a pressor substance. The association has been seen in more than 40 population studies (Ascherio et al., 1996): Some show a linear relationship through-out the entire range of consumption; others show a J-shaped relationship, with slightly less hyper-tension in individuals who consume fewer than two drinks per day as compared to those who abstain (Shaper et al., 1988) (Fig. 3-39). As much as 10% of hypertension in men can be attributed directly to alcohol excess (MacMahon, 1987). Those who drink large quantities of alcohol only on weekends have a higher 24-hour ambulatory BP on Monday than on Thursday, whereas those who drink daily have similar BPs on both days (Rakic et al., 1998). When heavy drinkers quit or reduce their intake, their BP usually goes down (Xin et al., 2001).

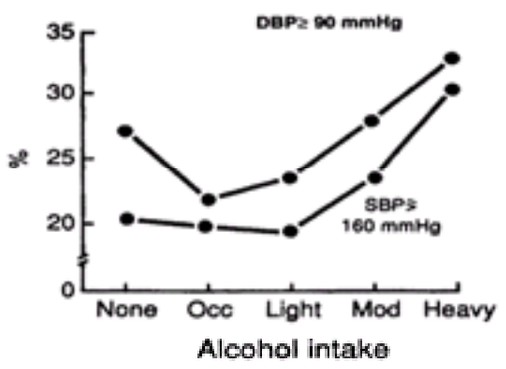

FIG. 3-39. Age-adjusted prevalence rates (%) of measured systolic and diastolic hypertension by levels of alcohol intake in drinks. DBP, diastolic blood pressure; Occ, occasional drinking; Light, one or two drinks daily; Mod, moderate (three to six drinks daily); Heavy, more than six drinks daily; SBP, systolic blood pressure. (Reprinted from Shaper AG, Wannamethee G, Whincup P. Alcohol and blood pressure in middle-aged British men. *J Hum Hypertens* 1988;2:71S–78S, with permission.)

The J-shaped pattern shown in Figure 3-39 parallels the association with total and coronary mortality. In most studies, mortality from coronary disease is lower with moderate alcohol consumption (fewer than two drinks per day of any type of alcoholic beverage) (Goldberg et al., 2001). Some do not find this association and ascribe the lower mortality reported in other studies to the likelihood of a better socioeconomic status of light drinkers (Hart et al., 1999). Stroke mortality is increased only with heavy consumption (Wannamethee and Shaper, 1996). These same relations hold for hypertensive patients as well, with the lowest mortality seen with consumption of one to ten standard-sized alcohol portions per week (Palmer et al., 1995).

Possible Mechanisms

The pressor effects of alcohol may arise from the following:

- Alterations of cell membranes, allowing more calcium to enter and magnesium to leave, perhaps by inhibition of sodium transport (Hsieh et al., 1995).
- Stimulation of SNS activity (Randin et al., 1995).
- Induction of insulin resistance with subsequent hyperinsulinemia, the lower BPs noted among light consumers possibly being related to improved insulin sensitivity (Kiechl et al., 1996).
- Increases in cortisol secretion, which can lead to a pseudo-Cushing's appearance in some heavy drinkers (Kirkman and Nelson, 1988).

Physical Inactivity

The critical importance of physical activity to prevent obesity and insulin resistance was noted earlier in this chapter. This protection may reflect the finding that regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation (DeSouza et al., 2000).

People who are physically active and fit are less likely to develop hypertension, and those who are hypertensive may lower their BP by regular isotonic exercise (Blumenthal et al., 2000). Normotensive people who were at a low level of physical fitness, as assessed by maximal treadmill testing, had a 52% greater relative risk for developing hypertension over the following 1 to 12 years as compared to people who were initially at a high level of physical fitness (Blair et al., 1984).

Temperature and Altitude

BP tends to be higher in colder weather (Jansen et al., 2001), which may play a role in the increase in cardiovascular mortality seen during the winter months (Khaw, 1995). Similarly, ascent to higher altitude may raise the BP (Wolfel et al., 1994), and more hypertension may be seen among those who live at higher altitudes (Khalid et al., 1994).

ASSOCIATIONS WITH HYPERTENSION

In addition to all of these possible mechanisms, surveys of large populations reveal a number of associations with hypertension that are likely not directly causal but are reflective of shared mechanisms (e.g., glaucoma) or of consequences of the hypertension (e.g., hyperuricemia).

Hyperuricemia

Hyperuricemia is found in as many as one-half of untreated hypertensives, and gout is more common (Bradlow, 1998). Some find naturally occurring (Fang and Alderman, 2000) or diuretic-induced (Franse et al., 2000) hyperuricemia to be associated with increased cardiovascular disease. Although no such relation was found in the Framingham Heart Study (Culleton et al., 1999), hyperuricemia often is found in patients at increased cardiovascular risk from dyslipidemia and other features of insulin resistance or metabolic syndrome, as hyperinsulinemia stimulates the renal reabsorption of urate (Puig and Ruilope, 1999).

Hematologic Findings

Red Cells

Probably related to decreased plasma volume, higher hematocrits are found in hypertensives and are associated with abnormal left ventricular filling on echocardiography (Schunkert et al., 2000). In the young subjects in the Tecumseh study, higher hematocrits were associated with higher BP, weight, cholesterol, glucose, and insulin levels (Smith et al., 1994). In middle-aged subjects in England, the risk of stroke was three times higher in hypertensives with a hematocrit above 51% than in those with a lower hematocrit (Wannamethee et al., 1994).

White Cells

Elevated white blood cell counts are predictive of the development of hypertension (Friedman et al., 1990) and are likely related to insulin resistance and hyperinsulinemia (Facchini et al., 1992). In the Framingham population, higher white blood cell counts were associated with an increased risk of cardiovascular disease (Kannel et al., 1992).

Platelets

Platelet counts usually are normal, but an increase in concentrations of vasoconstrictor purine dinucleotides has been found in platelets from hypertensives (Hollah et al., 2001).

Fibrinogen

Elevated plasma fibrinogen levels are a major risk factor for coronary heart disease (Yarnell et al., 1991) and have been noted in hypertensives with insulin resistance (Landin et al., 1990) or reduced renal function (Catena et al., 2000).

Hypofibrinolysis

Decreased fibrinolytic activity, reflected by increased levels of plasminogen activator inhibitor and tissue plasminogen activator antigen, was directly related to BP levels in the Framing-ham offspring population (Poli et al., 2000). Such impaired fibrinolysis obviously could increase the likelihood of thrombotic complications (Lip and Blann, 2000).

Viscosity

Not surprisingly, in view of the findings just noted, whole-blood viscosity is increased by approximately 10% in untreated mild hypertensives, comparable to the increase in their PR (Devereux et al., 2000). Increased blood viscosity along with increased hematocrits and thrombogenic factors may be involved in the greater threats of thrombotic rather than hemorrhagic complications in hypertensive patients.

Sex Hormones

Menopause

Women have a rising incidence of hypertension after menopause, which is associated with a major increase in cardiovascular risk (Kitler, 1992). A simple explanation for the increased incidence of hypertension after menopause is that the monthly menses keeps fluid volume slightly lower in women before menopause so that the hemodynamic cascade toward hypertension is slowed (Seely, 1976).

Estrogen

Premenopausal women with hypertension usually have a higher heart rate and CO and a lower PR than do men with similar degrees of hyper-tension (Messerli et al., 1987). These differences could reflect higher estrogen levels, which have been found to be even higher in premenopausal hypertensive women than in normotensive subjects (Hughes et al., 1989). In that same study, estrogen levels were also higher in hypertensive than in normotensive men, although still well below those in

women.

Testosterone

Hypertensive men have been reported to have lower testosterone levels than normotensive men (Barrett-Connor and Khaw, 1988).

Other Associations

The following conditions have been found to have an increased association with hypertension:

- Acute intermittent porphyria (O'Mahoney and Wathen, 1996)
- Aortic stenosis (Ie et al., 1996)
- Birth date in autumn (Banegas et al., 2000)
- Blood group MN (Delanghe et al., 1995)
- Cancer incidence (Chow et al., 2000; Gross-man et al., 2000)
- Color blindness (Morton, 1975)
- Exposure to radio-frequency electromagnetic field (Braune et al., 1998)
- Hypoalgesia (Ghione, 1996)
- Hypertensive spouse (Hippisley-Cox and Pringle, 1998)
- Keloids (Dustan, 1995)
- Open-angle glaucoma (Fraser et al., 1996)
- Pseudoxanthoma elasticum (Parker et al., 1964)
- Reduced forced vital capacity (Selby et al., 1990)
- Senile cataracts (Clayton et al., 1980)
- Serum IgG levels (Khraibi, 1991)
- Turner syndrome (Nathwani et al., 2000)

A number of other diseases in which accompanying hypertension frequently is noted are described in Chapter 15.

CONCLUSION

The preceding coverage may not exhaust the possible mechanisms for primary hypertension, but it at least touches on all that have received serious attention to date. It should be reemphasized that multiple defects likely are involved, and some of the initiating factors may no longer be discernible, having been dampened as hypertension develops. Without specific genetic markers, it is impossible to know whether a normotensive person, even with a strongly positive family history, will definitely develop hypertension, so that long-term prospective studies are difficult to design and perform.

In the absence of certainty about the pathogenesis of hypertension, it will be difficult to convince many patients that preventive measures should be undertaken. However, there seems no possible harm and a great deal of potential good to be gained from moderation in intake of sodium, calories, and alcohol; maintenance of good physical condition; and avoidance of unnecessary stress. As is described in Chapter 6, the value of these preventive measures has been demonstrated.

Now that the possible causes of primary hypertension have been examined, we turn to the natural history and clinical consequences of the disease. Regardless of cause, its consequences must be addressed.

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4
Primary Hypertension: Natural History and Evaluation

Now that the possible causes of primary hyper-tension have been considered, we turn to its clinical course and complications. We will first view the natural history of the disease if left untreated, examining the specific manner by which hypertension leads to premature cardiovascular damage and how such damage is clinically expressed. Additional coverage is provided for special populations—the elderly, women, blacks and other ethnic groups, diabetics, the obese—who may follow somewhat different courses. Based on this background, guidelines for evaluating the newly diagnosed hypertensive patient are presented.

As will be noted in more detail later in this chapter, isolated systolic hypertension (ISH) becomes the predominant form of hypertension in persons over age 60. Because this reflects arterial stiffening from atherosclerosis, it comes as no surprise that more atherosclerotic cardiovascular disease accompanies ISH, developing over a shorter interval than is characteristic of the progression of combined systolic-diastolic hypertension in younger patients, which is the focus of the first part of this chapter.

NATURAL HISTORY OF PRIMARY HYPERTENSION

The natural history of hypertension, depicted in Figure 4-1, starts when some combination of hereditary and environmental factors sets into motion transient but repetitive perturbations of cardiovascular homeostasis (*prehypertension*), not enough to raise the blood pressure (BP) to levels defined as abnormal but enough to begin the cascade that, over many years, leads to BPs that usually are elevated (*early hypertension*). Some people, abetted by lifestyle changes, may abort the process and return to normotension. The majority, however, progress into *established hypertension*, which, as it persists, may induce a variety of complications identifiable as target organ damage and disease.

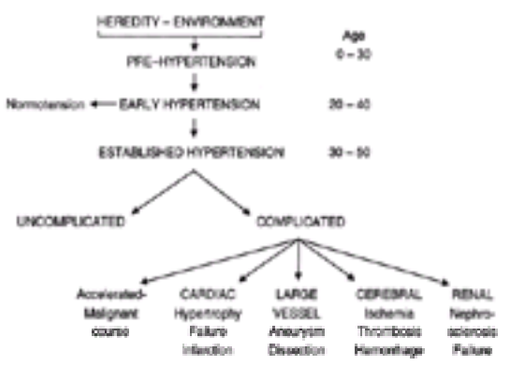


FIG. 4-1. Representation of the natural history of untreated essential hypertension.

As was noted in Chapter 1, the higher the BP and the longer it remains elevated, the greater the morbidity and mortality. Although some patients with markedly elevated, untreated BP never have trouble, we have no way of identifying in advance those who will have an uncomplicated course, the few who will enter a rapidly progressing, accelerated-malignant phase, and the many who will more slowly but progressively develop cardiovascular complications.

The role of hypertension probably is underestimated from morbidity and mortality statistics, which are largely based on death certificates. When a patient dies from a stroke, a heart attack, or renal failure—all directly attributable to uncontrolled hypertension—the stroke, the heart attack, or the renal failure, *not* the hyper-tension, usually is listed as the cause of death.

PREHYPERTENSION

As the pathogenetic mechanisms discussed in Chapter 3 start the process that leads to hyper-tension, certain clues may predict that the patient is in the prehypertensive phase. One clue is low birth weight (Roseboom et al., 2001); others include:

- *Exaggerated rises of BP during stress or exercise.* Based on an average of 8.8 years' follow-up of healthy normotensive men, it has been noted that those who developed hyper-tension were three times more likely than matched controls to have had an exaggerated BP response during a graded maximal exercise test (Matthews et al., 1998).
- *BPs that are in the higher ranges of normal.* As perhaps best seen in data from the Framingham cohort shown in Figure 4-2, the BP tends to track over many years, remaining in the same relative position over time (Kotchen et al., 1982). After an initial regression toward the mean between the first examination and the

second, 2 years later subjects in each BP segment tend to remain in that segment, with a slow, gradual rise over the 14 years of follow-up. In a later survey of the Framingham population, hypertension developed over a 4-year interval in only 5% of men and women with optimal BP (<120/80 mm Hg), in 18% with a normal BP (<130/85 mm Hg), and in 37% with a high-normal BP (130–139/85–89 mm Hg) (Vasan et al., 2000).

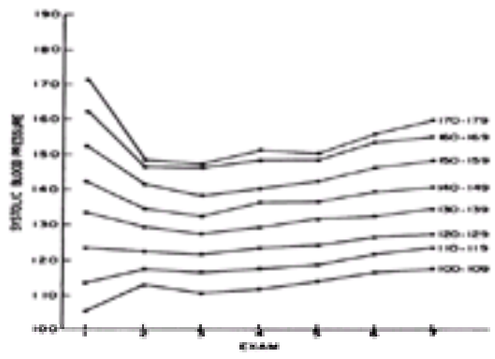


FIG. 4-2. Mean systolic blood pressure levels measured every 2 years on repeated examinations of Framingham study men, aged 30 to 59 years, divided into groups by their initial levels of blood pressure. Those taking antihypertensive drugs are excluded. [Reprinted from Kotchen JM, McKean HE, Kotchen TA. Blood pressure trends with aging. *Hyper-tension* 1982;4(Suppl 3):128–134, with permission.]

- *Presence of causal or coincidental features.* In the 30-year observation of the Framingham offspring, the major contributors to the incidence of hypertension beyond age were adiposity, heart rate, alcohol intake, hematocrit; blood glucose; and serum protein, triglyceride, and phosphorus levels, the last having a negative correlation (Garrison et al., 1987). As described in Chapter 3, the distribution of body fat played a significant role, with a markedly higher incidence of hypertension among those with more upper body fat as determined by subscapular skinfold thickness. As in all other populations, the strongest predictor was the previous level of BP, but weight gain is the next strongest predictor, both in children (Bao et al., 1995) and in adults (Bakx et al., 1999).

EARLY HYPERTENSION: COURSE OF THE BLOOD PRESSURE

In most people who become hypertensive, the hypertension persists, but in some the BP returns to normal, presumably not to rise again. As emphasized in Chapter 2, hypertension should be confirmed by multiple readings before the diagnosis is made and therapy is begun. Initial readings may be higher than subsequent readings because of a greater alerting reaction and, as with all biologic variables, a tendency for initially higher readings to come down from regression toward the mean. If subsequent readings are considerably lower and the patient is free of obvious vascular complications, the patient should be advised to adhere to a healthy lifestyle and either to return every few months for repeat BP measurement or to self-monitor the BP at home.

The wisdom of this course is shown by data from the Australian therapeutic trial (Management Committee, 1982); 12.8% of the patients whose diastolic BPs averaged more than 95 mm Hg on two sets of initial readings obtained 2 weeks apart had a subsequent fall to less than 95 mm Hg that persisted over the next year, such that the patients could not be entered into the trial. An even larger portion (47.5%) of those who entered the trial with a diastolic BP above 95 mm Hg and who received only placebo tab-lets for the next 3 years maintained their average diastolic BP at less than 95 mm Hg. A significant portion remained below 90 mm Hg while on placebo, including 11% of those whose initial diastolic BP was as high as 105 to 109 mm Hg. Overall, 80% of those on placebo maintained a diastolic BP of less than 100 mm Hg and, during the average 3-year follow-up, had no excess morbidity or mortality. On the other hand, 12.2% of the placebo-treated patients experienced a progressive rise in diastolic BP to more than 110 mm Hg.

From these data and others that will be described, a number of implications can be made:

- Multiple BP readings over at least 6 weeks may be needed to establish the diagnosis of hypertension.
- Many patients who are not given antihypertensive drugs will have a significant decline in their BP, often to levels considered safe and not requiring therapy.
- Patients who are free of target organ damage and whose diastolic BPs are lower than 100 mm Hg and certainly lower than 95 mm Hg can safely be left off active drug therapy for at least a few years.
- If not treated, patients should be kept under close observation.

These conclusions form part of the basis of the approach toward initial management of patients with relatively mild hypertension that is presented in Chapter 5.

ESTABLISHED HYPERTENSION

As delineated in Chapter 1 and shown in Figure 1-1, the long-term effects of progressively higher levels of BP on the incidence of stroke and coronary heart disease (CHD) are clear: In nine prospective observational studies involving 420,000 people with diastolic BP ranging from 70 to 110 mm Hg who were followed up for 6 to 25 years, the associations were “positive, continuous and apparently independent” (MacMahon et al., 1990).

Uncontrolled Long-Term Observations

In addition to these major studies, smaller groups of patients with fairly severe hypertension were followed up by investigators before effective therapies became available (Bechgaard, 1983; Ranges, 1949; Simpson and Gilchrist, 1958). Perera (1955) followed up 500 patients with a causal diastolic BP of 90 mm Hg or higher—150 patients from before disease onset and 350 from an uncomplicated phase— until their death. The incidence of complications is given in Table 4-1. The mean age of onset was 32 years, and the mean survival time was 20 years. Perera (1955) summarized his survey of the natural history of hypertension as follows:

Complication	Percent affected	Mean survival after onset (yr)
Cardiac		
Hypertrophy seen by radiograph	74	8
Hypertrophy seen by electrocardiography	59	6
Congestive heart failure	50	4
Angina pectoris	16	5
Cerebral		
Encephalopathy	2	1
Stroke	12	4
Renal		
Proteinuria	42	5
Elevated blood urea nitrogen	18	1
Accelerated phase	7	1

Data from Perera GA. Hypertensive vascular disease: description and natural history. *J Chron Dis* 1955;1:33–42.

TABLE 4-1. *Complications in 500 untreated hypertensives*

> . . . a chronic illness, more common in women, beginning as a rule in early adult life, related little if at all to pregnancy, and persisting for an average period of two decades before its secondary complicating pathologic features cause death at an average age fifteen to twenty years less than the normal life expectancy. Hypertensive vascular disease may progress at a highly variable rate, but on the whole the patient with this disorder spends most of his hypertensive life with insignificant symptoms and without complications.

Age of Onset

One additional point about Perera's data is worth emphasizing: Few of his patients experienced the onset of hypertension after age 45. A similar finding was observed in the Cooperative Study of Renovascular Hypertension, wherein the diagnosis of primary hypertension was made with even greater certainty in 1,128 patients

(Maxwell, 1975). Of these, the onset of an elevated BP was documented to have occurred at an age younger than 20 years in 12% and older than 50 years in only 7% (Maxwell, 1975).

On the other hand, in a more recent prospective study of a large, more representative population than the one followed up by Perera or seen in the Cooperative Study, 20% of people aged 40 to 69 years who developed a diastolic BP of 90 mm Hg or higher over a 5-year period were 60 years of age or older (Buck et al., 1987). More-over, the rate of developing a significant cardiovascular event among the newly discovered hypertensives was almost as high among those in their forties as among those aged 60 to 65 years (Table 4-2). Note that the middle-aged hypertensives were much more likely to develop an event than were normotensives of the same age but, as Buck et al. (1987) stated, "age overtakes hyper-tension as a cause of cardiovascular disease," so that among those aged 60 to 65, there was little difference in the rate.

Age group (yr)	Rate per 100[a]		
	New hypertensive	Normotensive	Odds ratio
40–49	4.6 (239)	0.9 (4,677)	5.2
50–59	5.6 (288)	3.2 (3,655)	8.0
60–65	6.5 (153)	5.7 (1,301)	1.2

[a]Number of subjects is shown in parentheses.
Data from Buck C, Baker P, Bass M, Donner A. The prognosis of hypertension according to age at onset. *Hypertension* 1987;9:204–208.

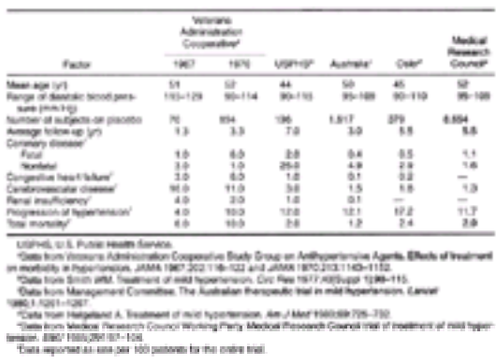
TABLE 4-2. *Five-year occurrence of cardiovascular events in newly diagnosed hypertensive subjects and normotensive subjects by age and baseline*

Prognosis in Women

In all these series, women have shown a better prognosis: Fewer women enter the accelerated-malignant phase or suffer from CHD. However, as women live longer, CHD along with hyper-tension (Rosenthal and Oparil, 2000) becomes increasingly more common and is now the leading cause of death in postmenopausal women (Wenger, 1997).

Untreated Patients in Clinical Trials

To those patients left untreated during the 1940s and 1950s when no effective therapy was readily available we can add those patients who served as the control populations in the trials of the therapy of hypertension up to the mid-1990s, at which time placebo-controlled trials were no longer considered ethical. Although these trials were not designed to observe the natural history of hypertension, their data can help to define further the course of untreated disease (Table 4-3). The trials involving elderly patients will be considered separately.



Factor	Veterans Administration Cooperative[a]		USPHS[b]	Australia[c]	Oslo[d]	Medical Research Council[e]
	1967	1970				
Mean age (yr)	51	52	44	50	45	52
Range of diastolic blood pressure (mm Hg)	115–129	90–114	90–115	95–109	90–110	95–109
Number of subjects on placebo	70	894	196	1,917	379	8,894
Average follow-up (yr)	1.3	3.3	7.0	3.0	5.5	5.6
Coronary disease[f]						
Fatal	1.0	6.0	2.0	0.4	0.5	1.1
Nonfatal	3.0	1.0	25.0	4.9	2.9	1.6
Congestive heart failure[f]	3.0	6.0	1.0	0.1	0.2	—
Cerebrovascular disease[f]	10.0	11.0	3.0	1.5	1.5	1.3
Renal insufficiency[f]	4.0	3.0	1.0	0.1	—	—
Progression of hypertension[f]	4.0	10.0	17.0	12.1	17.2	11.7
Total mortality[f]	6.0	10.0	3.0	1.2	2.4	2.8

USPHS, U.S. Public Health Service.
[a]Data from Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. *JAMA* 1967;202:116–122 and *JAMA* 1970;213:1143–1152.
[b]Data from Smith WM. Treatment of mild hypertension. *Circ Res* 1977;40(Suppl 1):98–115.
[c]Data from Management Committee. The Australian therapeutic trial in mild hypertension. *Lancet* 1980;1:1261–1267.
[d]Data from Helgeland A. Treatment of mild hypertension. *Am J Med* 1980;69:725–732.
[e]Data from Medical Research Council Working Party. Medical Research Council trial of treatment of mild hypertension. *BMJ* 1985;291:97–104.
[f]Data reported as rate per 100 patients for the entire trial.

TABLE 4-3. *Complications among control groups in trials of nonelderly hypertensives*

The types of patients included in these randomized, controlled trials (RCTs) and the manner in which they were followed up differ considerably, so comparisons between them are largely inappropriate. Moreover, the patients enrolled in these RCTs were, in general, much healthier than the general population. In most, they had to be free of major debilities and, often, any coexisting diseases, such as diabetes. For example, only 1.1% of those screened were eligible for enrollment in the Systolic Hypertension in the Elderly Program (SHEP) trial (SHEP Cooperative Research Group, 1991). Therefore, the rate of complications seen during the few years of follow-up on no therapy can be considered the minimum. In the overall population, much higher rates of cardiovascular diseases would be expected, and the dangers of untreated hypertension would obviously expand over a longer time.

Veterans Administration Cooperative Study Group on Antihypertensive Agents

Publications of the data of the Veterans Administration Cooperative Study Group on Antihypertensive Agents (1967, 1970, 1972) are landmarks in the field of clinical hypertension. The Veterans Administration (VA) study involved a selected population—male veterans who were reliable and cooperative—but the data probably are applicable to most moderately severe hypertensives.

Diastolic Blood Pressure between 115 and 129 mm Hg

The first VA study described the course of 70 men with an initial diastolic BP between 115 and 129 mm Hg who received only placebo. During their follow-up, which averaged 16 months and ranged up to 3 years, these complications were noted:

- Four patients died, three from ruptured aortic aneurysms.
- Seventeen patients developed accelerated hypertension, cerebral hemorrhage, severe congestive heart failure (CHF), or azotemia.
- Six patients developed myocardial infarction (MI), milder congestive failure, cerebral thrombosis, or transient ischemic attacks.

Thus, in less than 3 years, almost 40% of the patients with diastolic BP between 115 and 129 mm Hg who were *initially without severe target organ damage* developed complications.

Diastolic Blood Pressure between 90 and 114 mm Hg

As surprising as the results just described were at the time, even more dramatic were the findings in the 194 patients with initial diastolic BP of 90 to 114 mm Hg, a group considered to have mild to moderate hypertension (VA Cooperative Study, 1970, 1972). Their initial BPs averaged 157/101 mm Hg, and just more than half had some evidence of preexisting hypertensive complications. Maximal follow-up was 5.5 years and averaged 3.3 years. The overall risk to these patients of developing a morbid event in a 5-year period was 55%.

All the various complications except progression into accelerated hypertension occurred more frequently in the patients older than 60 years: Sixty-three percent

developed a serious complication during this short interval, as compared to 15% of the patients younger than 50 years. Another 14% of the younger patients had a significant rise in their diastolic BP to more than 124 mm Hg, so that without therapy they would be expected to develop complications quickly.

These results showed a more serious and rap-idly progressive course of untreated mild to moderate essential hypertension than had been suggested by most previously reported studies. Even among those who had no preexisting tar-get organ damage, 16% developed a complication in only 5 years.

U.S. Public Health Service Hospital Study

In the U.S. Public Health Service (USPHS) study (Smith, 1977), 389 patients with hypertension milder than that of the patients in the VA study were randomly divided into placebo and drug treatment groups and were followed up for as long as 7 years. At the onset of hypertension, none of the patients had evidence of target organ damage, and their mean BP was only 148/99 mm Hg. During the 7-year follow-up, the complications listed in Table 4-3 were noted among the placebo-treated group of truly mild hypertensives, con-firming the conclusions of the VA study.

Australian Therapeutic Trial

As previously noted, in the Australian therapeutic trial, more than 1,600 adults with diastolic BP of 95 to 109 mm Hg on two sets of readings obtained 2 weeks apart and initially free of known cardiovascular diseases were kept on placebo for an average of 3 years (Management Committee, 1980). Over this relatively short period, significantly increased morbidity and mortality occurred only in those whose diastolic BP averaged 100 mm Hg or higher. Recall, however, that 12.2% of these patients had a progressive rise in diastolic BP to more than 110 mm Hg (Table 4-3).

Oslo Trial

The smaller Oslo trial (Helgeland, 1980) was similar to the Australian therapeutic trial in that it included only patients with uncomplicated disease who were free of target organ damage with a diastolic BP of less than 110 mm Hg and randomly divided them into nontherapy and drug therapy groups. The two trials differed in that the Oslo trial involved only men younger than 50 years. The results were very similar in both trials. In the Oslo trial, approximately half of the non-treated group experienced a fall in diastolic BP during the first 3 years. Few complications developed among those whose diastolic BP was initially below 100 mm Hg, whereas 16.4% of those whose initial diastolic BP was between 100 and 110 mm Hg had a cardiovascular complication.

Medical Research Council Trial

For the Medical Research Council trial (1985) , half of a large group of men and women aged 35 to 64 years whose diastolic BP ranged from 90 to 109 mm Hg were randomly assigned to placebo tablets or active drugs for an average of 5.5 years. Their rates of subsequent events and progression to more severe hypertension were similar to those in the other trials of mild to moderate hypertension (Table 4-3).

Untreated Elderly Patients in Trials

Table 4-4 summarizes data from seven RCTs of elderly hypertensives, two of them [SHEP (1991) and the Systolic Hypertension in Europe Trial (Staessen et al., 1997)] including only patients with ISH, the others including a portion with ISH. The control patients in these trials had much higher rates of the various end points than were seen in the trials of younger hypertensives listed in Table 4-3.

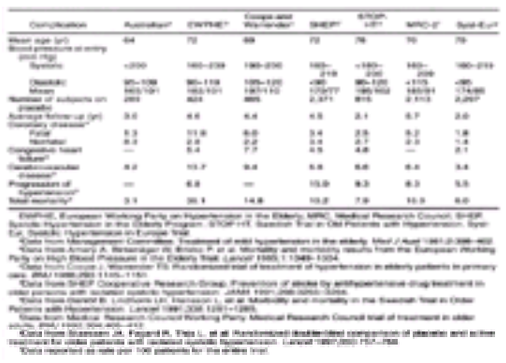


TABLE 4-4. *Complications among control groups in trials of elderly hypertensives*

An additional analysis has examined the experience of patients 80 years and older in all eight trials that included such patients (Gueyffier et al., 1999). Not surprisingly, the untreated hypertensives over age 80 experienced even higher rates of morbidity and mortality than those seen in Table 4-3 and Table 4-4 for younger patients. Among the 796 control patients followed for an average 3.5 years, the numbers of events were as follows: 77 strokes, 64 heart failures, and 223 deaths.

Systolic versus Diastolic Pressure

As noted in Chapter 1, the metaanalysis of all published trials of elderly patients (Staessen et al., 2000) reconfirmed what has been repeatedly shown in multiple observational studies: Rises in systolic levels and falls in diastolic levels, with the resultant widening of pulse pressure, are both typical changes that occur with aging and the major predictor of risk. As shown in Figure 4-3, risk of death rises steeply for every increment of systolic BP but, at every level of systolic BP, the risk increases further the lower the diastolic BP.

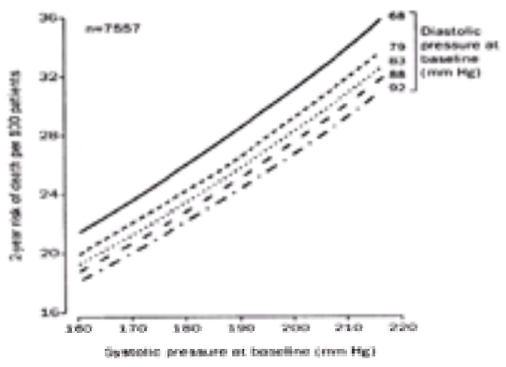


FIG. 4-3. The 2-year probability of death associated with systolic blood pressure at different levels of diastolic pressure at baseline in untreated elderly women with isolated systolic hypertension but no prior cardiovascular complications enrolled in eight randomized, con-trolled trials. (Reprinted from Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly. *Lancet* 2000;355:865–872, with permission.)

From these multiple sources, the picture of the natural history of hypertension shown in Figure 4-1 is derived. We now will examine the various complications shown

at the bottom of that figure.

COMPLICATIONS OF HYPERTENSION

The end of the natural history of untreated hypertension is an increased likelihood of pre-mature disability or death from cardiovascular disease. Before considering the specific types of organ damage and the causes of death related to hypertension, the underlying basis for the arterial pathology caused by hypertension and the manner in which this pathology is expressed clinically will be examined.

As described in Chapter 3, the pathogenesis of hypertension involves structural changes in the resistance arterioles subsumed under the terms *remodeling* and *hypertrophy*. These same changes almost certainly are also involved in the development of the small-vessel arteriosclerosis that is responsible for much of the target organ damage seen in long-standing hypertension. At the same time, the high shear stress accelerates large-vessel atherosclerosis (Malek et al., 1999). Such arterial and arteriolar sclerosis may be considered secondary consequences of typical combined systolic-diastolic hypertension, whereas arterial sclerosis is primarily responsible for the predominantly systolic hypertension so common among the elderly.

Types of Arterial Lesions

The more common vascular lesions found in hypertension are:

- Fibrinoid necrosis, seen with acute and severe rises i
- Hyperplastic or proliferative arteriolar sclerosis.
- Hyaline arteriolar sclerosis, with thickening and hyalinization of the intima and media.
- Miliary aneurysms in small cerebral penetration arterioles, usually at their first branching, which represent poststenotic dilations beyond areas of intimal thickening and which, when they rupture, cause the cerebral hemorrhages so typical of hypertension.
- Atherosclerotic plaques where thrombi form and which likely are responsible for the ischemia and infarction of heart, brain, kidney, and other organs that occur more frequently among hypertensives.

Other defects in the media of arteries (such as those at the circle of Willis that cause subarachnoid hemorrhages) may be accentuated by hypertension but probably are congenital. Medial damage in the wall of the aorta may lead to the formation of large plaques with eventual aneurysmal dilation and rupture. The process of cystic medial necrosis that is responsible for some aortic dissections also occurs more frequently in hypertensives.

Atherosclerosis

Most of the premature morbidity and mortality associated with hypertension is related to atherosclerosis. Although usually only one of the multiple risk factors involved, hypertension has an independent role (Agmon et al., 2000) that is present even in the earliest manifestations of atherosclerosis in young people (Berenson et al., 1998).

As reviewed by Ross (1999), “The lesions of atherosclerosis represent a series of highly specific cellular and molecular responses that can best be described, in aggregate, as an inflammatory disease.” Rather than the previous concept of a response to injury, “which initially proposed that endothelial denudation was the first step, the most recent version emphasizes endothelial dysfunction rather than denudation.” Hypertension is obviously among the possible causes of such endothelial dysfunction.

Ross (1999) ascribes a major role to angiotensin II as contributing to atherogenesis by stimulating the growth of smooth muscle. “Hypertension also has proinflammatory actions, increasing the formation of hydrogen peroxide and free radicals. . . . These substances reduce the formation of nitric oxide by the endothelium, increase leukocyte adhesion, and increase peripheral resistance” (Ross, 1999).

In a previous attempt to explain the role of hypertension in vascular damage, Chobanian (1990) indicated that hyperlipidemia was integral to the formation of atherosclerosis (Fig. 4-4). Ross (1999) considered hypercholesterolemia to be important in only about half of patients with cardiovascular disease, concluding that “atherosclerosis is clearly an inflammatory disease and does not result simply from the accumulation of lipids.”

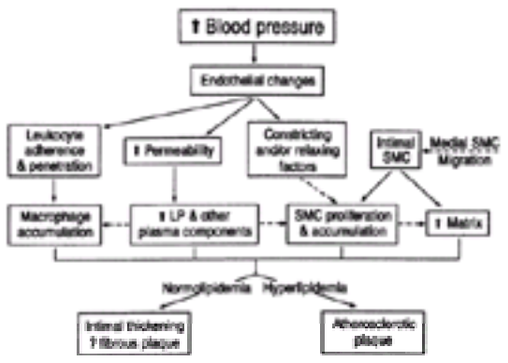


FIG. 4-4. Diagram summarizing the effects of hypertension on the arterial intima., increased; LP, lipoprotein; SMC, smooth muscle cell. (Reprinted from Chobanian AV. 1989 Corcoran Lecture: adap-tive and maladaptive responses of the arterial wall to hypertension. Hypertension 1990;15:666–674, with permission.)

As another explanation for the vascular dam-ages seen with hypertension, Hamet et al. (2001) have proposed

> that a proliferative process may be primarily involved in hypertension development. . . . with an imbalance of proliferation and apoptosis in later stages. . . . [There is] evidence of a nonlinear, dichotomous process so that cardiovascular cells from hypertensive subjects are subjected to accelerated turnover, potentially culminating in accelerating aging.

Causes of Death

Death may result when these arterial lesions either rupture or become occluded enough to cause ischemia or infarction of the tissues they supply. The overall increase in mortality associated with hypertension was examined in Chapter 1; Table 4-5 provides a more detailed look at the causes of death in hypertensives, mostly from series published before the availability of effective therapy. The series in the table include different types of patients, so comparisons between them should be avoided.

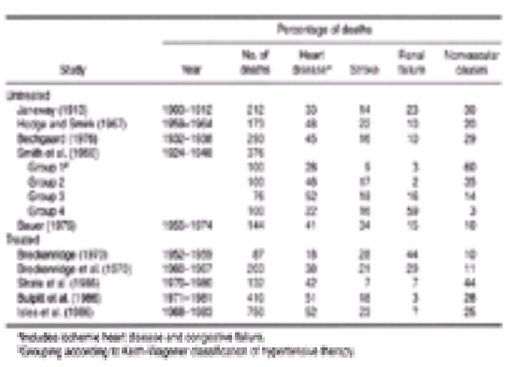


TABLE 4-5. *Causes of death in primary hypertension*

The following conclusions can be drawn from these data:

- As shown in the data from Smith et al. (1950), cardiovascular diseases are responsible for a higher proportion of deaths as the severity of the hypertension worsens.
- In general, patients with severe, resistant disease die of strokes; those presenting with advanced retinopathy and renal damage die of renal failure; and the majority, with moderately high BP, die of the complications of ischemic heart disease.
- Heart disease remains the leading cause of death.

As will be detailed in Chapter 5, with effective therapy of hypertension, strokes are pre-vented to a greater degree than is coronary disease, and heart failure is at least delayed.

TARGET ORGAN INVOLVEMENT

Having tabulated the major causes of death resulting from the arterial pathology related to hypertension, we will now examine in more detail the pathophysiology and consequences of these various complications. Thereafter, the clinical and laboratory manifestations of the target organ damage will be incorporated into guide-lines for evaluating the hypertensive patient.

In general, the complications of hypertension can be considered either hypertensive or atherosclerotic (Table 4-6). Those listed as hypertensive are caused more directly by the increased level of the BP per se, whereas the atherosclerotic complications have multiple causes, with hypertension playing a variable role (Berenson et al., 1998). However, the major contribution of hypertension to the atherosclerotic diseases is shown clearly by epidemiologic data, perhaps best from the ongoing Framingham study (Kannel, 1996) (Fig. 4-5).

Hypertensive complications
Accelerated-malignant hypertension (grades III and IV retinopathy)
Encephalopathy
Cerebral hemorrhage
Left ventricular hypertrophy
Congestive heart failure
Renal insufficiency
Aortic dissection
Atherosclerotic complications
Cerebral thrombosis
Myocardial infarction
Coronary artery disease
Claudication syndromes

Data from Smith WM. Treatment of mild hypertension. *Circ Res* 1977;40(Suppl 1):98–105.

TABLE 4-6. *Complications of hypertension*

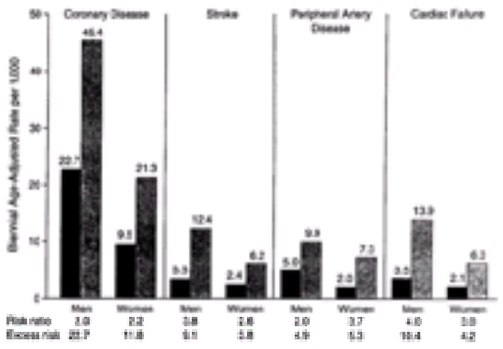


FIG. 4-5. Risk of cardiovascular events by hypertensive status in subjects aged 35 to 64 years from the Framingham study at 36-year follow-up. Coronary disease includes clinical manifestations such as myocardial infarction, angina pectoris, sudden death, other coronary deaths, and coronary insufficiency syndrome; peripheral artery disease is manifested as intermittent claudication. Left bars in each set of columns represent normotensives; right bars represent hypertensives. (Reprinted from Kannel WB. Blood pressure as a cardiovascular risk factor. *JAMA* 1996;275:1571–1576, with permission.)

Hypertensive Heart Disease

As seen in Figure 4-5, hypertension more than doubles the risk for symptomatic coronary disease, including acute MI and sudden death, and more than triples the risk for CHF (Kannel, 1996). The consequences reflect an admixture of effects directly induced by the hypertrophic response of the left ventricle to the increased afterload imposed by hypertension, [i.e., left ventricular hypertrophy (LVH)] and the acceleration of atherosclerosis through various paths (Ross, 1999).

Systolic and Diastolic Dysfunction

Diastolic and systolic dysfunction have been observed early in the course of hypertension, and either or both may lead to heart failure. In a 5-year follow-up of young, normotensive off-spring of hypertensive parents, those who developed mild hypertension also developed Doppler echocardiographic alteration of left ventricular (LV) diastolic function without a distinct increase in LV mass (Aeschbacher et al., 2001). Such diastolic dysfunction may reflect more vigorous atrial emptying (Ahmed et al., 2001) or abnormal diastolic relaxation (de Simone et al., 2000a). In established hypertension, abnormal relaxation has been observed in two-thirds of patients with normal LV systolic function (Rusconi et al., 2001).

The spectrum of diastolic dysfunction covers, on the one end, only a failure of LV enddiastolic volume to rise appropriately with exercise, all the way to the other end of left ventricular heart failure with normal systolic function. Nearly half of CHF patients turn out to have normal LV systolic function and are therefore defined as having diastolic heart failure (Vasan and Levy, 2000).

Although enhanced LV systolic function has been reported in young subjects with borderline hypertension, de Simone et al. (1996) have pointed out that studies that show LV ejection fraction and fractional shortening measured at the endocardium to be normal or supranormal may reflect a “conceptual mismatch,” as the mean level of LV end-systolic stress is applied at the level of the LV midwall, not at the endocardium. They found that assessment of midwall fiber shortening in relation to end-systolic LV wall stress identified depressed LV performance and increased cardiovascular risk (de Simone et al., 1994). When followed up for an average of 10 years, those hypertensives with decreased LV myocardial midwall performance had more adverse events, particularly when combined with higher LV mass (de Simone et al., 1996). In two recent large studies of young, mild hypertensives, a depression of LV systolic function was found in 8.9% (Palatini et al., 1998) and 17.5% (Schillaci et al., 2000b) in the absence of clinical overt heart disease.

Left Ventricular Hypertrophy

This brings us to the issue of LVH, the most common cardiac abnormality in hypertension. Some increase in LV mass can be seen even among children with BPs that are in the upper twentieth percentile but are not elevated (Hansen et al., 1992). In normotensive adults, LV mass is directly related to the risk for developing subsequent hypertension (de Simone et al., 1991a; Post et al., 1994), suggesting that LVH may be involved in the pathogenesis of the disease.

Prevalence

Whereas LVH is identified by electrocardiography in only 5% to 10% of hypertensives, LVH is found by echocardiography in nearly 30% of unselected hypertensive adults and in up to 90% of persons with severe hypertension (Schmieder and Messerli, 2000). More LVH is seen with obesity, high dietary sodium intake, anemia of end-stage renal disease, alcohol abuse, diabetes, and hypercholesterolemia (de Simone et al., 2001; Schmieder and Messerli, 2000). On the other hand, cardiac hypertrophy in response to excess load is nonpathologic in three circumstances: maturation in infancy and childhood, pregnancy, and high-level exercise (Lorell and Carabello, 2000).

Pathogenesis

When the heart faces a hemodynamic overload, the major compensation is an increase in muscle mass (Lorell and Carabello, 2000). In their words:

> A mechanical signal initiates a cascade of biological events leading to coordinated cardiac growth. . . . Within hours after a pressure over-load occurs, myosin heavy chain synthesis increases by about 35%. . . . If hypertrophy were perfectly regulated, changes in radius, thickness, and pressure would be orchestrated such that wall stress would be constantly normalized. However, this often does not occur (Lorell and Carabello, 2000).

LV mass has been found to be more closely related to systolic than to diastolic BP; the opposite is true for LV wall thickness (Schmieder and Messerli, 2000). Neurohormonal responses involving both the sympathetic and reninangiotensin systems may be recruited to increase contractility and participate in the hypertrophic response. Aldosterone increases collagen content and thereby influences adaptation and structural remodeling independent of BP levels (Weber et al., 1994).

An important role of the renin-angiotensin system is suggested by the impressive effect of angiotensin-converting enzyme inhibitors in causing regression of LVH and preventing remodeling after an MI (Pfeffer et al., 1992), particularly because all components of the system are in cardiac tissue, where their expression is regulated by local stress (Lee et al., 1996). Further evidence for a critical role of the reninangiotensin system is the close correlation of their circulating levels to LV mass (Harrap et al., 1996; Schmieder et al., 1996) and the recognition of a close connection between LVH and a deletion polymorphism of the angiotensinconverting enzyme gene, the DD genotype, which increases plasma angiotensin-converting enzyme activity (Schunkert et al., 1994).

Patterns

The patterns of LVH shown in Figure 4-6 differ by the type of hemodynamic load: Volume over-load leads to eccentric hypertrophy, whereas pure BP overload leads to an increase in LV wall thickness without concomitant increase in cavity volume (i.e., concentric hypertrophy). The pattern of LVH can also be modified by increased arterial stiffness, increased pulse-wave velocity, and blood viscosity.

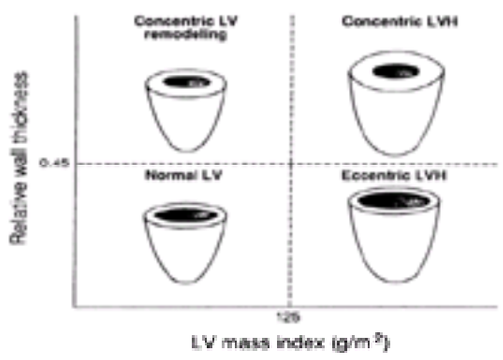


FIG. 4-6. Schematic diagram showing classification of left ventricular (LV) geometry based on level of its mass and relative wall thickness. Patients with increased LV mass are divided into those with eccentric or concentric LV hypertrophy (LVH), depending on whether they have normal or increased relative wall thickness; those with normal LV mass are similarly divided into groups with normal LV geometry or concentric LV remodeling. (Reprinted from Devereux RB, Roman MJ, Ganau A, et al. Cardiac and arterial hypertrophy and atherosclerosis in hypertension. *Hypertension* 1994;23:802–809, with permission.)

In Wachtell et al.'s (2001) series of 913 patients with varying stages of hypertension, these percentages of various patterns were found by echocardiography: 19%, normal geometry; 11%, concentric remodeling; 47%, eccentric hypertrophy; and 23%, concentric hypertrophy.

These different patterns of LVH have different features, hemodynamic relations, and prognostic implications (Devereux et al., 1994). Although some find that the geometric patterns do not add much additional prognostic information beyond that offered by the simple degree of LVH and traditional cardiovascular risk factors (Verdecchia et al., 1996), Devereux (1995) stoutly defends the seriousness of concentric hypertrophy, including evidence for its association with more arterial dysfunction (Roman et al., 1996).

Consequences

The presence of LVH is consistently and strongly related to subsequent cardiovascular morbidity (mean risk ratio, 2.3) and mortality (mean risk ratio, 2.5) (Vakili et al., 2001). Specific associations have been noted between LVH and CHD (Brown et al., 2000; Schillaci et al., 2000a), carotid atherosclerosis (Okin et al., 1996), stroke (Bikkina et al., 1994), funduscopic and renal damage (Shigematsu et al., 1995), and sudden death (Haider et al., 1998). The increased risk for sudden death in hypertensives is likely connected to complex ventricular arrhythmias associated with LVH (Saadeh et al., 1999).

Even without LVH, early hypertensives may have a significantly reduced coronary flow reserve from an impaired capacity for coronary vasodilation (Palombo et al., 2000). With LVH, the threshold for myocardial ischemia may be lowered in at least two ways in addition to the simple increase in demand for blood flow imposed by the larger mass of muscle: first, by further reducing the ability of the coronary circulation to vasodilate, which may, in turn, be secondary to small-vessel disease (Iriarte et al., 1995), and second, by shifting the lower range of coronary flow autoregulation upward (Harrison et al., 1988). Both of these alterations reduce coronary reserve (Devereux et al., 2000; Strauer, 1992), making the heart vulnerable to ischemia when demand increases or when perfusion pressure is reduced (Guazzi, 1995) (Fig. 4-7). This latter situation is obviously involved in the J-curve of increased coronary ischemic events that may develop as diastolic BP is reduced below approximately 85 mm Hg (see Chapter 5).

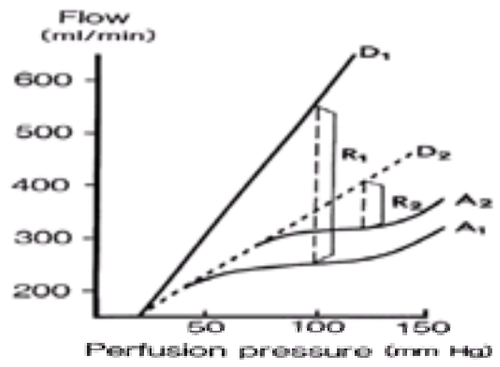


FIG. 4-7. Pressure-flow relationships in the normal left ventricle (A_1,D_1) and the hypertrophied, hypertensive left ventricle (A2,D2) during auto-regulation (A) and maximal vasodilatation (D). In the hypertrophied hypertensive left ventricle, coronary flow reserve (R2) is lower than in the normal ventricle (R1), even if the perfusion pressure is higher, and the lower range of autoregulation is shifted to higher perfusion pressure. (Reprinted from Guazzi MD. Left ventricular hypertrophy in hypertension, coronary micro-and macrovascular disease, and myocardial ischemia. *Cardiovasc Risk Factors* 1995;5:133–139, with permission.)

Regression

Because the presence of LVH connotes a number of deleterious effects of hypertension on cardiac function, a great deal of effort has been expended in showing that treatment of hypertension will cause LVH to regress. This will be explored further in Chapter 7, in which the effects of various agents are covered. With regression, LV function improves (Muiesan et al., 2000) and the long-term risk of cardiovascular events appears to be reduced (Verdecchia et al., 1998).

Congestive Heart Failure

The various alterations of systolic and diastolic function seen with LVH obviously can progress into CHF. Hypertension is present in 91% of patients who develop CHF, triple the risk of normotensives (Levy et al., 1996). Hypertension remains the major preventable factor in the disease that is now the leading cause of hospitalization in the United States for adults over age 65 (Kannel, 2000a). It is likely that antihypertensive treatment does not completely prevent CHF but postpones its development by several decades (Kannel, 2000a).

Most episodes of CHF in hypertensive patients are associated with systolic dysfunction, as reflected in a reduced ejection fraction. However, approximately 40% of episodes of CHF are associated with diastolic dysfunction and preserved LV systolic function (Vasan and Levy, 1996). For example, in a series of patients with acute pulmonary edema and systolic BP above 160 mm Hg, an exacerbation of diastolic dysfunction, rather than systolic dysfunction, was responsible in almost half (Gandhi et al., 2001). Vasan and Benjamin (2001) explain the susceptibility of hypertensives, particularly those with LVH, to diastolic heart failure:

> When hemodynamically challenged by stress (such as exercise, tachycardia, increased afterload, or excessive preload), persons with hypertension are unable to increase their end-diastolic volume (i.e., they have limited preload reserve), because of decreased LV relaxation and compliance. Consequently, a cascade begins, in which the LV end-diastolic BP rises, left atrial pressure increases, and pulmonary edema develops.

Management of CHF in hypertensive patients is covered in Chapter 7.

Coronary Heart Disease

As described in Chapter 1, hypertension is quantitatively the largest risk factor for CHD. The development of myocardial ischemia reflects an imbalance between myocardial oxygen supply and demand. Hypertension, by reducing the sup-ply and increasing the demand, can easily tip the balance.

Mechanisms

Hypertension is associated with multiple factors that accelerate CHD, including

- Acceleration of atherosclerotic narrowing of larger coronary arteries (Nitenberg and Antony, 1996).
- Impaired endothelium-dependent vasodilation (Perticone et al., 1999).
- Limited coronary reserve, with or without LVH (Palombo et al., 2000).

Clinical Manifestations

These multiple mechanisms render hypertensives more susceptible to coronary ischemia (Asmar et al., 1996), MI, and sudden death (Kannel, 1996). Hypertensives suffer more silent ischemia (Boon et al., 2000) and painless MI (Kannel et al., 1985) than do normotensives, perhaps because they have a lower sensitivity to pain (Airoldi et al., 2000).

Hypertension may play an even greater role in the pathogenesis of CHD than is commonly realized, because preexisting hypertension may go unrecognized in patients first seen after an MI. Although acute rises in BP may follow the onset of ischemic pain (McAlpine et al., 1988), the BP often falls immediately after the infarct if pump function is impaired.

Once an MI occurs, the prognosis is affected by both the preexisting and the subsequent BP. The 28-day case fatality rate among 635 men who had an acute MI was 24.5% in those with a prior systolic BP below 140 mm Hg, 35.6% with a prior systolic BP of 140 to 159 mm Hg, and 48.2% with a prior systolic BP of 160 mm Hg or higher (Njølstad and Arnesen, 1998). On the other hand, an increase in post-MI mortality has been noted among those whose BP fell significantly, presumably a reflection of poor pump function (Flack et al., 1995). If the BP of these subjects remained elevated, the prognosis was even worse, likely representing a severe load on a damaged myocardium, so that care must be taken with patients who have either lower or higher BP after an infarction.

A particular concern when thrombolytic therapy is given for acute MI is the threat for stroke that is imposed by the presence of hypertension. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries–I (GUSTO-I) trial, the incidence of stroke went from 1.2% for normotensives to 3.4% in those with systolic BP greater than 175 mm Hg (Aylward et al., 1996).

Large-Vessel Disease

Abdominal Aortic Aneurysm

The incidence of abdominal aortic aneurysms is increasing, likely as a consequence of the increasing number of elderly people (van der Vliet and Boll, 1997). Although hypertension is a risk factor for aortic aneurysm (Blanchard et al., 2000), ultrasonography uncovered such an aneurysm in only 3% of mild hypertensives aged 60 to 75 years but in 11% of those with systolic BP above 195 mm Hg and either cerebral or peripheral vascular disease (Simon et al., 1996).

Aortic Dissection

As many as 80% of patients with aortic dissection have hypertension (Lindsay, 1992). The mechanism of dissection likely involves the combination of high pulsatile wave stress and accelerated atherosclerosis, because the higher the pressure, the greater the likelihood of dissection.

Aortic dissection may occur either in the ascending aorta (proximal, or type A), which requires surgery, or in the descending aorta (distal, or type B), which usually can

be treated medically (Prêtre and von Segesser, 1997). Hypertension is more frequently a factor with distal dissections, whereas Marfan's syndrome and cystic medial necrosis are seen more frequently with the proximal lesion (Lindsay, 1992).

Peripheral Vascular Disease

The presence of symptomatic peripheral vascular disease, usually manifested by intermittent claudication, poses a high risk of subsequent cardiovascular mortality (Criqui et al., 1992). Measurement of the ankle-arm BP index by a Doppler device is an objective way to diagnose and stratify the risk of peripheral vascular disease (Abbott et al., 2000).

Takayasu's Disease

Hypertension is present in nearly half of patients with Takayasu's disease, a chronic inflammatory disease of large arteries that is reported most frequently in Japan and India (Kandarpa et al., 1991). Antiendothelial cell antibodies, found in 18 of 19 patients, may serve as a diagnostic test (Eichhorn et al., 1996).

Cerebrovascular Disease

Each year approximately 750,000 people in the United States have a stroke, making stroke the third most common cause of death after heart disease and cancer (Williams et al., 1999). The stroke death rate is even higher (by approximately 50%) among blacks who live in the southeastern United States. (Obisesan et al., 2000), a rate similar to that noted in numerous other groups with inadequate healthcare world-wide (Sarti et al., 2000). Mortality rates from stroke have fallen markedly over the last 40 years in most industrialized countries (Omae et al., 1994; Tuomilehto et al., 1996) but the long-term decline seems to have stopped in the United States (Gillum and Sempos, 1997). In some areas, the incidence has risen, likely because of the larger number of elderly people and the introduction of computed tomography, which increases the detection of smaller strokes (Brown et al., 1996). However, in southern Sweden, a marked increase in the incidence of first stroke occurred from 1983 through 1985 to 1993 through 1995, mainly in people younger than 75 (Johansson et al., 2000).

Role of Hypertension

Even more than with heart disease, hypertension is the major cause of stroke. As noted by Phil-lips and Whisnant (1992):

> A wealth of epidemiological evidence indicates that hypertension is the most important modifiable risk factor for transient ischemic attacks, ischemic stroke, and focal intracerebral hemorrhage. Epidemiological observation and laboratory experimentation have shown that hypertension predisposes to stroke by (1) aggravating atherosclerosis in the aortic arch and cervicocerebral arteries; (2) causing arteriosclerosis and lipohyalinosis in the small-diameter penetrating cerebral end arteries; and (3) promoting heart disease that may be complicated by stroke.

In hypertensives, nearly 80% of strokes are ischemic, caused by either arterial thrombosis or embolism; 10% to 15% are caused by intraparenchymal hemorrhage; another 5% are caused by subarachnoid hemorrhage; and 5% to 15% are of unknown cause (Anderson et al., 1993; Bogousslavsky et al., 1996). Transient ischemic attacks—acute episodes of focal loss of cerebral or visual function lasting less than 24 hours and attributed to inadequate blood supply—may arise from emboli from atherosclerotic plaques and are closely associated with CHD (Brown et al., 1994).

As noted in Chapter 1, ISH in the elderly is associated with a two to four times greater incidence of strokes than is seen in normotensive people of the same age. Elderly hypertensives more often have silent cerebrovascular disease (Ikeda et al., 1994), which eventually may lead to brain atrophy and vascular dementia (Skoog et al., 1996).

There is a marked increase in the onset of ischemic stroke in the early morning hours after arising, when BP suddenly increases (Argentino et al., 1990). On the other hand, treated hypertensives whose BP dips during sleep may also be more vulnerable (Morfis et al., 1997). Even among hypertensives on antihypertensive treatment, as many as half of the strokes are attributable to uncontrolled BP (Klungel et al., 2000), particularly in patients over age 70 (Makino et al., 2000).

Whether hypertensive or normotensive before their stroke, the majority of stroke patients at the time they are first seen will have a transient elevation of BP that spontaneously falls within a few days (Morfis et al., 1997). Therefore, caution is advised in lowering the BP in the immediate poststroke period, as noted further in Chapter 7.

Extracranial Carotid Disease

Increasing thickness of the intima-media of the carotid arteries, usually assessed by B-mode ultrasonography, is a measure of preclinical atherosclerosis and is directly associated with both stroke and coronary disease (Chambless et al., 2000). As expected, carotid disease is more common in hypertensives, even more in whites than in blacks (Wityk et al., 1996). Those with symptoms or bruits should have noninvasive studies and consideration given to endarterectomy for those with high-grade stenoses (Paciaroni et al., 2000).

Cognitive Impairment and Dementia

Hypertension is associated with impaired cognition even in the absence of clinically evident cerebrovascular disease (Rigaud et al., 2000). The direction of the association may be dependent on age: Cognitive impairment is related to hypertension at least up to age 70 (Kilander et al., 1998); in subjects older than 75, the stronger relationship is to low BP, likely a reflection of extensive atherosclerosis (Steward, 1999).

Vascular dementia is strongly related to prior hypertension but, as the dementia worsens, BP often diminishes (Rigaud et al., 2000). There appears to be an inverse relation between the occurrence of Alzheimer's disease and hyper-tension (Guo et al., 1996), and the presence of low BP (<130/70 mm Hg) increases mortality in elderly people with dementia (Guo et al., 1998).

Renal Disease

Renal dysfunction, both structural and functional, is often demonstrable in hypertensive patients, even those with minimally elevated BPs. Pathologically, the main changes of milder degrees of hypertension are hyalinization and sclerosis of the walls of the afferent arterioles, referred to as *hypertensive nephrosclerosis* (Fogo et al., 1997).

Manifestations

Renal involvement usually is asymptomatic, with loss of concentrating ability manifested as nocturia oftentimes being the first indication. The first objective sign is microalbuminuria (Rosa and Palatini, 2000), serving as a marker for impaired intrarenal vasodilative responsiveness (Mimran et al., 1994) and as a likely factor in the initiation and progression of tubulointerstitial damage (Gangevoort et al., 1997). Most easily assessed by measurement of the albumin-creatinine ratio in a random urine sample (Post et al., 2000), microalbuminuria is a predictor not only of progressive renal damage but also of overall cardiovascular morbidity (Gerstein et al., 2001; Jensen et al., 2000). Heavy proteinuria even to the nephrotic range can occur (Innes et al., 1993).

Questions about the Role of Hypertension

Despite fairly strong epidemiologic evidence for an association between hypertension and renal disease (Whelton et al., 1997), some investigators question the relationship (Ljungman, 1999). They believe that the renal damage seen in hypertensives is secondary to underlying primary renal diseases, such as focal segmental glomerulosclerosis, that may, in turn, be aggravated by the presence of hypertension (Howie, 1996). Beevers and Lip (1996) note that renal dysfunction developed infrequently during the various RCTs of the treatment of hypertension, just as infrequently in those treated as in those given placebo. They state, “We know of no reported cases of benign essential hypertensive patients with normal serum-creatinine levels and no proteinuria who subsequently went on to develop renal failure” (Beevers and Lip, 1996).

The issue remains unsettled. It is true that only a small minority of hypertensives develop progressive renal insufficiency; on the other hand, the incidence rises

progressively with every increment in BP (Klag et al., 1997). All agree that the likelihood for development of this condition is greater in diabetics and in blacks (Perry et al., 1995). Although the markedly greater likelihood of the diagnosis of hypertensive nephrosclerosis as the cause of end-stage renal disease in blacks is partly the result of inaccurate labeling (Freed-man et al., 1995), renal biopsies confirm this diagnosis in most nondiabetic hypertensive blacks with mild to moderate renal insufficiency (Fogo et al., 1997). However, with careful analysis of all known risk factors, hypertension has been identified as the primary cause of end-stage renal disease in only 10% of blacks in the United Kingdom (Fernandes et al., 2000) and the United States (Zarif et al., 2000). Fortunately, as will be noted in Chapter 9, aggressive treatment of hypertension in those with renal insufficiency will usually slow its progression (Ruilope et al., 2001).

As will be emphasized in Chapter 9 and Chapter 10, renovascular disease must always be remembered as a not infrequent cause of renal insufficiency and hypertension (Textor and Wilcox, 2000).

Summary

In every patient, the damage from hypertension to the various target organs that have been described should be assessed to determine the need for therapy and to ensure that therapy protects the most vulnerable parts of the cardiovascular system.

NATURAL HISTORY OF SPECIAL POPULATIONS

Before turning to evaluation, I will describe groups of people whose hypertension, for various reasons, may follow a different course from that seen in the predominantly male, white, middle-aged populations observed in most clinical trials and long-term observational studies. These special groups include a major part of the hypertensive population: the elderly, women, blacks and other ethnic groups, diabetics, and the obese.

Elderly

Two patterns of hypertension are seen in the elderly: combined systolic and diastolic—the carryover of primary (essential) hypertension common to middle age—and ISH—the more frequent form in those over age 60. However, because the major consequences and, as is noted in Chapter 7, the therapy for both are quite similar, most of this discussion will not make a distinction between the two.

Prevalence of Hypertension

As noted in Figure 1-3 in Chapter 1, whereas diastolic BPs tend to plateau before age 60 and drop thereafter, systolic BPs rise progressively. Therefore, the incidence of ISH—defined as systolic pressure of 140 mm Hg or more and diastolic pressure of 90 mm Hg or less— progressively rises with age. In the National Health and Nutrition Examination Survey III, the proportion of various types of hypertension seen with advancing age progressively shifted from diastolic and combined hypertension to ISH (Franklin et al., 2001). In those older than 60 years, ISH was the pattern of hypertension in 87% of those who were untreated. In another population, 16% of patients with ISH had previous diastolic hypertension (Bulpitt et al., 1995). Systolic levels usually continue to rise after age 70 in those who remain healthy but tend to fall if chronic debilitating diseases occur (Starr et al., 1998).

As described in Chapter 2, two cautions are needed in evaluating BP levels in the elderly, First, the white-coat effect is more common and significant in the elderly than in younger people (Fotherby and Potter, 1993) so out-of-office readings should be obtained if possible. Second, the elderly may have artifactually elevated BPs by usual indirect cuff measurements (i.e., pseudohypertension) because of increased stiffness of the large arteries, which precludes compression and collapse of the brachial artery by the cuff (Spence, 1997).

Risks of Hypertension

The higher systolic BP and the lower diastolic BP that typically occur with aging obviously combine to widen the pulse pressure. Pulse pressure is slightly more robust than systolic BP as an indicator of risk, but it has not yet been validated as an end point for outcomes in RCTs, so the systolic BP is recommended as the measure of risk in the elderly (Izzo et al., 2000).

As seen in Table 4-4 in the data from the placebo-treated half of the elderly patients enrolled in seven RCTs over the last 20 years, mortality in elderly hypertensives is significant, particularly from strokes, even in the brief 2- to 5-year interval of these trials. As noted, the patients enrolled tend to be healthier than the general population, so the risks of both combined systolic-diastolic and ISH are even greater than shown in Table 4-4.

A different pattern appears in the very elderly who have chronic debility. In the subjects aged 75 to 94 years followed up in the Framingham study, risks for all-cause and cardiovascular mortality increased at lower levels of systolic BP (<120 mm Hg) (Fig. 4-8). Most of this increase occurred in those with existing cardiovascular disease. As Kannel et al. (1997) note:

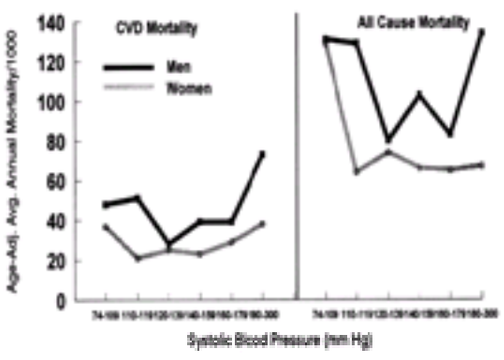


FIG. 4-8. All-cause and cardiovascular disease (CVD) mortality rates in systolic blood pressure in 75- to 94-year-old subjects in the Framingham Heart Study. (Modified from Kannel WB, D'Agostino RB, Silbershatz H. Blood pressure and cardiovascular morbidity and mortality rates in the elderly. Am Heart J 1997;134:758–763.)

> There appears to be a different morbidity and mortality rate curve in the elderly that appears to be quadratic (U-shaped) in those who have already had a cardiovascular event and linear in those free of cardiovascular disease. The excess mortality rate at low BP levels could be a reflection of poor ejection fractions rather than the impact of low BP. . . . It is thus likely that BP elevation remains a detrimental risk factor even in the very old.

In addition to increased mortality seen with either low systolic BP (<120–130 mm Hg) or high systolic BP (>180 mm Hg), both are associated with the development of cognitive impairment (Guo et al., 1997).

Pathophysiology of Isolated Systolic Hypertension

The basic mechanism for the usual progressive rise in systolic BP with age is the loss of distensibility and elasticity in the large capacitance arteries, a process that was nicely demonstrated more than 50 years ago (Hallock and Benson, 1937) (Fig. 4-9). Increasing volumes of saline were infused into the tied-off aortas taken from patients at death whose ages ranged from the twenties to the seventies. The pressure within the aortas from the elderly subjects rose much higher with small increases in volume as compared to that in aortas from the younger subjects, reflecting the rigidity of the vessels.

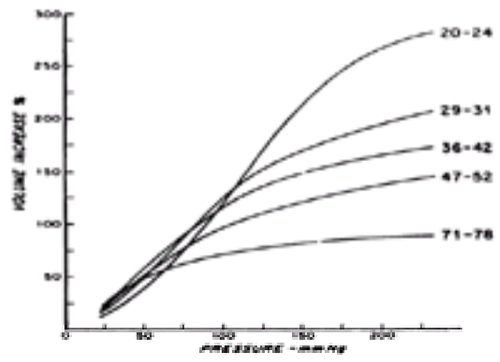


FIG. 4-9. Curves showing the relation of the percentage of increase in pressure to the increase in volume infused into aortas excised at autopsy from people in five different age groups. The curves were constructed from the mean values obtained from a number of aortas. (Reprinted from Hallock P, Benson IC. Studies of the elastic properties of human isolated aorta. *J Clin Invest* 1937;16:595–602, with permission.)

With more sophisticated techniques, Nichols et al. (1992) found a reduced cross-sectional area of the peripheral vascular bed and stiffer aorta and large arteries, producing an increased pulse-wave velocity and an early return of pulse-wave reflection in systole. The early return of the reflected pressure wave augments aortic pressure throughout systole, increasing both systolic and pulse pressure, further increasing the work of the left ventricle while decreasing the diastolic aortic pressure that supports coronary blood flow (Pierini et al., 2000).

Elderly patients with combined systolic and diastolic hypertension (as compared to younger hypertensives) have lower cardiac output, intravascular volume, renal blood flow, and plasma renin activity and higher peripheral vascular resistance, LV wall thickness, and mass (Messerli et al., 1983).

Postural Hypotension

As is covered in Chapter 7, therapy of hypertension in the elderly is vital but oftentimes must be tempered by the need first to overcome coexisting postural hypotension.

Definition and Incidence

A fall in systolic pressure of 20 mm Hg or more after 1 minute of quiet standing is defined as postural hypotension. In the generally healthy population of elderly men and women enrolled in the Systolic Hypertension in the Elderly Program, postural hypotension was found in 10.4% at 1 minute after rising from a seated position and in 12.0% at 3 minutes, with 17.3% having hypotension at one or both intervals (Applegate et al., 1991). The prevalence would likely have been higher if the patients had been tested after rising from a supine position. The only predisposing factor for postural hypotension found in an unselected elderly population was hypertension (Räihä et al., 1995). As seen in Figure 4-10, the higher the basal supine systolic BP, the greater was the tendency for a postural fall (Lipsitz et al., 1985).

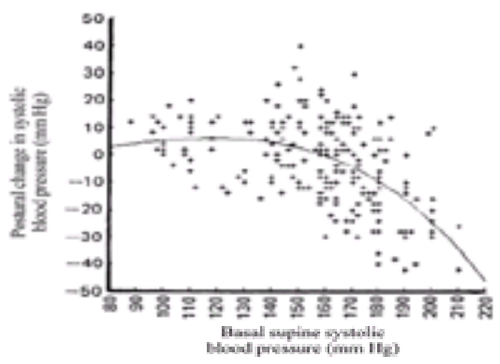


FIG. 4-10. Relationship between basal supine systolic blood pressure and postural change in systolic blood pressure for aggregate data from older subjects. (Reprinted from Lipsitz LA, Storch HA, Minaker KL, Rowe JW. Intra-individual variability of postural BP in the elderly. *Clin Sci* 1985:69:337–341, with permission.)

Mechanism

Normal aging is associated with various changes that may lead to postural hypotension. The two most common changes in patients with supine or seated hypertension are venous pooling in the legs and reduced baroreceptor sensitivity (Harrington et al., 2000). Even though elderly hypertensives have intact baroreceptor modulation of sympathetic nerve traffic, they have marked impairment of baroreceptor control of heart rate and of cardiopulmonary reflex control of the peripheral circulation (Grassi et al., 2000). In addition, splanchnic pooling of blood after eating may lead to profound postprandial hypotension (Puisieux et al., 2000).

Women

Before age 50, women have a lower prevalence of hypertension than do men. Although there is apparently no abrupt transition during menopause (Luoto et al., 2000), after age 60 hyper-tension is more prevalent in women (Rosenthal and Oparil, 2000). Premenopausal women have been found to have higher levels of basal nitric oxide synthesis than do men (Forte et al., 1998), which could help to explain their lower BPs. After age 50, women tend to become more obese, which could help to explain their higher incidence of hypertension and concentric LVH (Kuch et al., 1998), and a slowing of the decline in coronary disease that has been attributed to their reduction in smoking, improved diet, and use of hormone replacement therapy (Hu et al., 2000). Because women live longer than men and older women have such a high prevalence of hypertension, they contribute the larger share of the population's attributable risk for hypertension-related complications.

The roles of oral contraceptives and estrogen replacement therapy are covered in Chapter 11.

As an aside, women experience more white-coat hypertension than do men, which could explain the better outcomes observed in women when the diagnosis of hypertension is based on office BP measurements.

Hemodynamics

Hypertension in women is associated with a higher resting heart rate and cardiac index and lower total peripheral resistance than in men with similar BP levels (Messerli et al., 1987). As compared to men, older hypertensive women tend to have larger LV chambers and better LV function, higher levels of atrial natriuretic factor, and lower levels of plasma renin activity, all of which are compatible with a greater degree of fluid volume expansion (de Simone et al., 1991b).

Blacks

In brief, blacks have more hypertension and suffer more from it, largely because of their lower socioeconomic status and resultant reduced access to necessary health care. Their higher prevalence of hypertension likely reflects both genetic and environmental factors (El-Gharbawy et al., 2001). If appropriate therapy is provided, most of their excessive morbidity and mortality related to hypertension can be relieved.

Prevalence of Hypertension

Blacks in the United States

Adult blacks in the United States have higher BP levels and, therefore, more hypertension than do nonblacks (see Chapter 1). These higher readings develop during childhood and adolescence and are established by early adulthood; most of the higher BPs in young blacks are attributed to a larger body weight and size (Berenson et al., 1996). In the baseline examination of a longitudinal study involving 5,116 young black and white men and women aged 18 to 30 years, blacks had higher mean systolic and diastolic BPs than did nonblacks (Liu et al., 1989). After 7 years, the black-white differences increased, partly because of changes in lifestyle and body weight. Adjustments for age, education, body mass index (BMI), physical activity, and alcohol intake reduced the differences substantially (Liu et al., 1996). In middle age, blacks and whites have similar incidences of hypertension given the same baseline BP and BMI (He et al., 1998).

In addition to higher BPs, blacks in the United States and United Kingdom (Mayet et al., 1998) (but not in Africa) usually have higher sleeping BPs, as recorded by ambulatory monitoring (Profant and Dimsdale, 1999), even after adjustment for other factors that influence BP (Appel et al., 2000), suggesting that the U.S. black-white difference is not racial but environmental.

Blacks Outside the United States

In their survey of blacks in seven populations of African origin, Cooper et al. (1999) found the rates of hypertension to be 7% in rural Nigeria, 26% in Jamaica, and 33% in the United States. These higher rates were associated with increased BMI and sodium intake, suggesting "that being overweight, and the associated lack of exercise and poor diet, explains between 40 and 50% of the increased risk for hypertension that African-Americans face compared with Nigerians" (Coo-per et al., 1999). As in the United States, a higher rate of hypertension (10.3%) among urban Nigerian men was associated with greater obesity, particularly abdominal in location (Olatunbosun et al., 2000).

Pathophysiology of Hypertension

Table 4-7 lists some of the numerous genotypic and phenotypic features found in black hypertensives that may explain their higher prevalence and greater degree of target organ damage. Whatever else is responsible, poverty (Smith et al., 1998), racial discrimination (Krieger and Sidney, 1996), and barriers to health care (Hill et al., 1999) obviously are involved in the higher hypertension-related morbidity and mortality seen in U.S. blacks.


Genotype
Angiotensinogen (Cooper et al., 1999)
Epithelial sodium channel (Baker et al., 2000)
G protein (β_3-subunit (Dong et al., 1999)
Transforming growth factor-β1, (Suthanthiran et al., 2000)
Intermediate phenotype
Activation of intrarenal-renin system (Price et al., 2001)
Decreased kallikrein excretion (Sung et al., 2000)
Decreased nitric oxide–dependent and –independent vasodilation (Cardillo et al., 1999)
Decreased potassium intake (Morris et al., 1999)
Diabetes mellitus (Brancati et al., 2000)
Glomerular hyperfiltration (Kotchen et al., 2000)
Increased adrenergic vasoconstriction (Stein et al., 2000; Abate et al., 2001)
Increased circulating endothelin-1 (Ergul, 2000)
Increased sodium sensitivity (Luft et al., 1991)
Obesity (Jones, 1999)
Sodium-induced renal vasoconstriction (Schmidlin et al., 1999)
Phenotype
Aortic stiffness (Ferrera et al., 1999)
Congestive heart failure (Dries et al., 1999)
Left ventricular hypertrophy (Sherif et al., 2000)
Left ventricular systolic dysfunction (Devereux et al., 2001)
Microalbuminuria (Srinivasan et al., 2000)
Nephrosclerosis (Knox et al., 1982)
Stroke (Gillum, 1989)

TABLE 4-7. *Features of hypertension in blacks*

Slavery Hypothesis

An interesting extension of the genetic role has been popularized by Wilson and Grim (1991). They first confirmed that the BP of blacks in the northern portion of the Western Hemisphere was significantly higher than the BP of blacks in sub-Saharan Africa, the area from which most of the former had come (Wilson et al., 1991).

These differences between U.S. and African blacks have generally been attributed to the psychosocial stresses of living as an oppressed minority in the United States, with concomitant low socioeconomic status (James et al., 1996). However, U.S. blacks also display a tendency to retain sodium more avidly and thereby experience a greater rise in BP than do nonblacks when given salt loads (Weir, 1995). Helmer (1967), the first to note lower plasma renin levels in U.S. blacks than in nonblacks, speculated that such low renin levels could reflect a maladaptation of an enhanced ability of the kidney to conserve salt, an ability that was of great survival value to Africans living in a hot environment with little access to salt. This presumably genetic trait, of value to African blacks, was of no value to U.S. blacks who lived in a cooler environment and who had more than ample access to salt. On the contrary, their more avid renal sodium retention could serve as the instigator of volume expansion and hypertension.

Blackburn and Prineas (1983) suggested that the transatlantic voyage involved in the slave trade that brought most blacks to the Western Hemisphere could have introduced another genetic maladaptation. They conjectured that those African natives who could best conserve salt would be more likely to survive the exigencies of a long, hot journey beset with vomiting, diarrhea, and limited food and fluid intake. Because the survivors were better salt retainers, they would also develop more hypertension when salt was plentiful.

As attractive as the slavery hypothesis seems to be, it has been vigorously denied in all of its major parts by a Johns Hopkins historian (Curtin, 1992).

Stress

As described in Chapter 3, a large body of literature attests to an association between the stresses of low socioeconomic status and hyper-tension. A good example of the likely interaction between low socioeconomic status and a genetic trait is the finding that BP levels were significantly associated with darker skin color but only in those blacks in the lower levels of socioeconomic status (Klag et al., 1991).

Beyond low socioeconomic status, James et al. (1996) have long held to an influence of a coping strategy involving an active effort to manage the stressors of life by hard work and determination to succeed. They call this coping strategy *John Henryism*, after a legendary uneducated black folk hero who defeated a mechanical steam drill in an epic battle but then dropped dead from complete exhaustion.

Diet

Particularly among older black women, the higher prevalence of hypertension is correlated closely with obesity (Jones, 1999). Although they have greater sensitivity to sodium, blacks do not appear to ingest more sodium than do nonblacks (Ganguli et al., 1999). However, their intake of both potassium and calcium is lower (Langford and Watson, 1990). As noted in Chapter 3, one possible way that reduced calcium intake could raise BP is by a lower serum calcium level that causes a secondary stimulation of parathyroid hormone release, as higher parathyroid hormone levels have been identified in black hypertensive patients (Brickman et al., 1993). Moreover, if, as appears to be true, the hypertension of blacks is associated with volume expansion, a resultant increased excretion of calcium would further lower serum calcium levels and provoke increased parathyroid hormone secretion.

Responsiveness to Growth Factors

Dustan (1995) attempted to explain the increased prevalence of severe hypertension in blacks by hypothesizing an increased responsiveness to vascular growth

factors comparable to that noted in fibroblasts that form keloids, which are also more common in blacks.

Complications of Hypertension

Hypertension is not only more common in blacks, but is also more severe, less well man-aged and, therefore, more deadly. As best as can be ascertained, blacks at any given level of BP do not suffer more vascular damage than do nonblacks; rather, they display a shift to the right of the BP distribution, yielding a higher overall prevalence and a higher proportion of severe disease (Cooper and Liao, 1992).

Much of the excess morbidity and mortality found in U.S. blacks as compared to U.S. non-blacks is related to the lower socioeconomic status of blacks but, at every level of income, blacks have a higher mortality rate from hypertensive heart disease than do whites (Smith et al., 1998). Considerable variation in mortality from cardiovascular causes was found among blacks living in New York City, depending on their birthplace: Southern-born blacks had a 30% higher coronary mortality than did northeastern-born blacks and a four times higher coronary mortality than did Caribbean-born blacks (Fang et al., 1996).

Cardiac Disease

Blacks have more LVH than nonblacks with equal levels of BP and are at a higher risk for progression of systolic dysfunction (Dries et al., 1999). Although the overall prevalence of CHD may be lower among U.S. blacks than among nonblacks, mortality rates from CHD are now higher because of a lesser decline in death rates among blacks than among whites in the United States (Gillum, 1996).

Cerebrovascular Disease

Blacks have more strokes than do nonblacks, particularly if they are born in the southeastern United States (Lackland et al., 1999). All forms of cerebrovascular disease are more frequent in blacks, with even greater differences between the black and nonblack populations in the incidence of strokes that are more tightly connected with hypertension (i.e., small-vessel ischemic stroke) (Woo et al., 1999).

Renal Disease

As noted earlier in this chapter, hypertensive blacks are more likely to end up with end-stage renal disease than are hypertensive whites (Perry et al., 1995). Much of this increased risk for renal failure results from low socioeconomic status and limited access to health care (Krop et al., 1999), but a heightened susceptibility to renal damage is also involved (Youssef et al., 2000). When renal disease reaches the end stage, blacks are much less likely to have access to renal transplantation (Epstein et al., 2000).

Other Ethnic Groups

Much less is known about the special characteristics of other ethnic groups as compared to blacks in the United States, so only a few generalizations will be made about them.

Primitive versus Industrialized Environment

People of any race living a rural, more primitive lifestyle tend to ingest less sodium, remain less obese, and have less hypertension. When they migrate into urban areas and adapt more modern lifestyles, they ingest more sodium, gain weight, and develop more hypertension (Cooper et al., 1999). Rather dramatic changes in the prevalence of hypertension and the nature of cardiovascular complications have been seen when formerly isolated ethnic groups move to an industrialized environment, as seen among South Asians who move to England (Khattar et al., 2000).

Persistence of Ethnic Differences

Although environmental changes often alter BP and other cardiovascular traits, some ethnic groups preserve characteristics that presumably reflect stronger genetic influences. Examples include Bedouins in Israel (Paran et al., 1992) and Native Americans in the United States (Howard, 1996). Native American descendants, such as Mexican-Americans in San Antonio, have a lesser prevalence of hypertension, despite their high prevalence of obesity, diabetes, and insulin resistance (Haffner, 1996). Thus ethnic origins may work both ways: to increase the propensity toward hypertension or to protect against the threat.

Diabetes and Hypertension

As described in Chapter 3, diabetics have a significantly higher prevalence of hypertension than do nondiabetics. The combination markedly increases the risk of premature cardiovascular disease. Even a slightly elevated fasting glucose in association with hypertension increases 8-year cardiovascular disease mortality more than two-fold (Henry et al., 2001). With or without hyper-tension, type 2 diabetics display more diastolic (Poirier et al., 2001) and systolic (Palmieri et al.,2001) LV dysfunction. During a 16-year period, the diabetics in the Framingham study suffered almost twice as many strokes, three times more pared to nondiabetics (Kannel et al., 1990). All of these are increased further when hypertension accompanies diabetes (Sowers et al., 2001).

The microvascular complications, retinopathy in particular, also are increased by hypertension (Cignarelli et al., 1992). The course and management of diabetic nephropathy, now second only to coronary disease as the cause of death in diabetic hypertensives, is covered in Chapter 9; details about the treatment of hypertension in diabetics are covered in Chapter 7.

Obesity and Hypertension

Even in the absence of type 2 diabetes, obesity is one of the most common factors responsible for hypertension, as discussed in Chapter 3. In the National Health and Nutrition Examination Survey III, a progressive increase in the prevalence of hypertension was seen with increasing BMI at all ages (Thompson et al., 1999) (Fig. 4-11). The prevalence is increased further when the obesity is predominantly abdominal (Harris et al., 2000). The cardiovascular risks of these overweight people are increased further by their three- to fourfold greater prevalence of diabetes and almost doubled prevalence of hypercholesterolemia. In the elderly, the cardiovascular risks of obesity diminish, but abdominal obesity remains a risk factor for cardiovascular disease mortality (Baik et al., 2000).

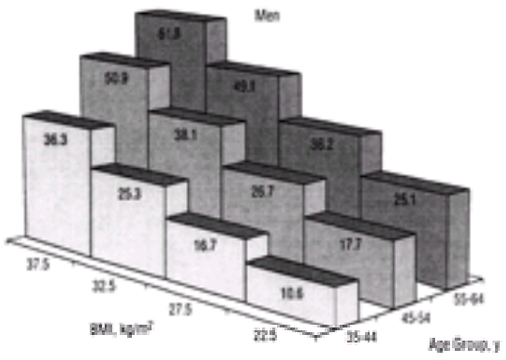


FIG. 4-11. Estimated risk (%) of hypertension by age group and body mass index (BMI) among men in the National Health and Nutrition Examination Survey III. (Modified from Thompson D, Edelsberg J, Colditz GA, et al. Lifetime health and economic con-sequences of obesity. *Arch Intern Med* 1999;159:2177–2183.)

Even after controlling for BP, obesity puts a load on the left ventricle, increasing LV mass and fibrosis, leading to diastolic dysfunction (Jain et al., 1996). In a 20-year

follow-up of more than 90,000 U.S. veterans, an increased initial BMI was associated with an increased risk of subsequent MI, CHF, and end-stage renal disease (Perry et al., 1997).

ALTERING THE NATURAL HISTORY

Now that the possible mechanisms, natural his-tory, major consequences, and special populations of untreated primary hypertension have been covered, an additional word about prevention is in order.

Most efforts to alter the natural history of hypertension involve both nondrug and drug therapy of existing disease. However, attempts to *prevent* hypertension must also be more widely promoted and followed. Without knowledge of the specific causes of this disease, no single preventive measure can be promoted with the assurance that it will work. However, to insist that specific causes be known before prevention is attempted is akin to saying that John Snow should not have closed the pump because he had no proof that *Vibrio cholera* organisms were the cause of death in those who drank the polluted water. The preventive measures likely to help—moderation in sodium intake, reduction of obesity, maintenance of physical conditioning, avoidance of stress, and greater attention to the other coexisting risk factors for premature cardiovascular disease— will do no harm and may do a great deal of good. These measures are covered in detail in Chapter 6.

EVALUATION OF THE HYPERTENSIVE PATIENT

Having examined the natural history of various hypertensive populations, we now incorporate these findings into a game plan for evaluating the individual hypertensive patient.

There are three main reasons to evaluate patients with hypertension: (a) to determine the type of hypertension, specifically looking for identifiable causes; (b) to assess the impact of the hypertension on target organs; and (c) to estimate a patient's overall risk profile for the development of premature cardiovascular disease. Such evaluation can be accomplished with relative ease and should be part of the initial examination of every newly discovered hypertensive. The younger the patient and the higher the BP, the more aggressive the search for identifiable causes should be. Among middle-aged and older persons, greater attention should be directed to the overall cardiovascular risk pro-file, as these populations are more susceptible than others to immediate catastrophe unless preventive measures are taken.

History

The patient history should focus on the duration of the elevated BP and any prior treatment, the current use of various drugs that may cause it to rise, and symptoms of target organ dysfunction (Table 4-8). Attention should also be directed toward the patient's psychosocial status, looking for such information as the degree of knowledge about hypertension, the willingness to make necessary changes in lifestyle and to take medication, and the ability to obtain sometimes expensive therapies. An area of great importance is sexual dysfunction, often neglected until it arises after antihypertensive therapy is given. Erectile dysfunction, often attributed to antihypertensive drugs, may be present in as many as one-third of untreated hypertensive men and is most likely related to their underlying vascular disease (see Chapter 7).

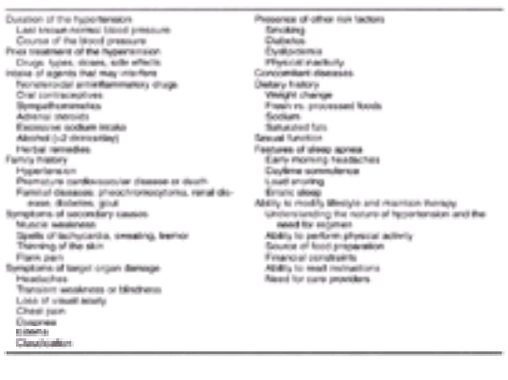


TABLE 4-8. *Important aspects of the patient's history*

Anxiety-Related Symptoms

Although many, if not most, hypertensives have symptoms that they ascribe to their elevated BP (Kjellgren et al., 1998), most of these symptoms are common to the functional somatic syndromes seen in people who believe they have a serious disease (Barsky and Borus, 1999). Many believe they can tell when their BP is elevated but, if so, the perception is likely from anxiety which, in turn, may be raising their BP (Cantillon et al., 1997). If questioned before they become aware of being hypertensive, symptoms including headaches, epistaxis, tinnitus, dizziness, and fainting were no more common among those with hypertension than among those with normal BP (Weiss, 1972).

This is in keeping with my belief that many of the symptoms described by hypertensives are secondary to anxiety over having “the silent killer” (as hypertension frequently is described), anxiety that often is expressed as recurrent acute hyperventilation or panic attacks (Davies et al., 1999). Many of the symptoms described by hypertensives, such as bandlike headaches, dizziness and lightheadedness, fatigue, palpitations, and chest discomfort, reflect recurrent hyperventilation, a common problem among all patients (DeGuire et al., 1992) but likely even more common among hypertensives who are anxious over their diagnosis and its implications (Kaplan, 1997).

Headache

Of the symptoms that are reported, headache is the most common but, again, mostly in those aware of the diagnosis. Stewart (1953) found that only 17% of patients unaware of their hypertension complained of headache, but among patients with similar levels of BP who were aware of their diagnosis, 71% had headaches.

This belief that headache is related not to the level of BP but rather to anxiety over the diagnosis of hypertension is strengthened by the fact that the prevalence of headache among newly diagnosed hypertensives varies little in relation to the level of BP, with 15% to 20% having headaches whether their diastolic BPs were as low as 95 mm Hg or as high as 125 mm Hg (Cooper et al., 1989). Moreover, headaches noted during ambulatory BP monitoring were not associated with simultaneous elevations in BP (Gus et al., 2001; Kruszewski et al., 2000).

Nonetheless, headaches were noted in 18% of men and 29% of women with a diastolic BP of 95 to 110 mm Hg who were enrolled in RCTs, and the overall prevalence was reduced from 22% to 17% after antihypertensive therapy (Hansson et al., 2000). With very high BP, head-aches do become more common. The headache is usually present on awakening, is felt in the back of the head, may or may not be throbbing in character, and often lasts only a few hours even without analgesic therapy. It should be noted that sleep apnea is common among even minimally obese hypertensives, as described in Chapter 15, so early morning headaches may reflect not hypertension but nocturnal hypoxia.

Nocturia

Nocturia is more common in hypertensives, often the consequence of coexisting benign pro-static hypertrophy (Blanker et al., 2000) or simply a decreased bladder capacity (Weiss and Blaivas, 2000). At least theoretically, the altered pressure-natriuresis relationship described in Chapter 3 could delay urinary excretion, and a loss of concentrating ability may be an early sign of renal impairment.

Physical Examination

The physical examination should include a careful search for damage to target organs and for features of various identifiable causes (Table 4-9). Waist circumference should be measured, because values exceeding 88 cm (34 in.) in women and 100 cm (39 in.) in men are indicative of abdominal obesity (Lemieux et al., 1996) and serve as a cardiovascular risk factor independent of weight (Turcato et al., 2000).

Accurate measurement of blood pressure
General appearance: distribution of body fat, skin lesions, muscle strength, alertness
Funduscopy
Neck: palpation and auscultation of carotids, thyroid
Heart: size, rhythm, sounds
Lungs: rhonchi, rales
Abdomen: renal masses, bruits over aorta or renal arteries, femoral pulses, waist circumference
Extremities: peripheral pulses, edema
Neurologic assessment, including cognitive function

TABLE 4-9. *Important aspects of the physical examination*

Funduscopic Examination

Only in the optic fundi can small blood vessels be seen with ease, but this requires dilation of the pupil, a procedure that should be more commonly practiced using a short-acting mydriatic such as 1% tropicamide.

Keith et al. (1939) originally classified the funduscopic changes but mixed two separate vascular changes: hypertensive neuroretinopathy (hemorrhages, exudates, and papilledema) and arteriosclerotic retinopathy (arteriolar narrowing, arteriovenous nicking, and silver wiring) (Sapira, 1984). Dodson et al. (1996) proposed a simpler grading system for hypertensive retinopathy: grade A, or nonmalignant—generalized arteriolar narrowing, focal constriction, and arteriovenous nicking; and grade B, or malignant—hemorrhages, hard exudates, and cotton-wool spots, with or with-out optic disc swelling (see Fig. 8-2).

With retinal photography, early changes are recognizable (Sever et al., 1997) even in children with mild hypertension (Daniels et al., 1993), and closer correlations between retinal changes and BP levels can be obtained (Sharrett et al., 1999). In one series, retinal hemorrhages and microaneurysms were seen in 9.8% of nondiabetic hypertensives, the prevalence directly related to the level of BP (Yu et al., 1998).

In usual nonophthalmologic clinical practice, however, funduscopic findings are of limited value, having only about a 60% positive or negative predictive value for the severity of hyper-tension (Fuchs et al., 1995). Certainly, the fundi should be examined in every new hypertensive and, if malignant changes are found, additional diagnostic studies and more aggressive therapy should be provided. If diabetes coexists, a full ophthalmoscopic examination should be per-formed yearly, as diabetic retinopathy is serious and treatable.

Laboratory Tests

Routine Laboratory Workup

For most patients, a hematocrit reading, urine analysis, automated blood chemistry (glucose, creatinine, electrolytes), lipid profile (total and HDL cholesterol, triglycerides), and electrocardiography are all the routine procedures needed. None of these usually yields abnormal results in the early, uncomplicated phases of primary hypertension, but they should always be obtained for a baseline.

Hypertriglyceridemia and, even more threatening, hypercholesterolemia are found more frequently in untreated hypertensives than in normotensives (Goode et al., 1995). As shown in Figure 4-12, the prevalence increases with the BP level (Bønaa and Thelle, 1991). The association may, in turn, reflect the metabolic syndrome of glucose intolerance, dyslipidemia, and hyper-tension likely related to insulin resistance and usually associated with abdominal obesity. Among 600 treated hypertensives aged 40 to 59 years, 91% had at least one of these additional risk factors (Rantala et al., 1999). In view of the remarkable benefits seen with statin therapy, which extend far beyond reduction in atherogenesis (Feron et al., 2001), the need to identify and treat dyslipidemia is even more critical.

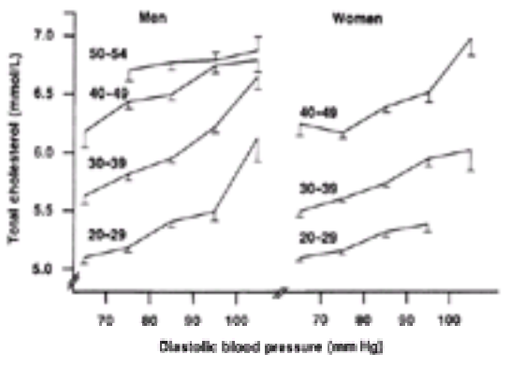


FIG. 4-12. Plot of mean concentrations of serum total cholesterol levels by diastolic blood pressure in 8,081 men, 20 to 54 years old, and in 7,663 women, 20 to 49 years old. T bars represent standard error of the mean. (Reprinted from Bønaa KH, Thelle DS. Association between blood pressure and serum lipids in a population. Circulation 1991;83:1305–1314, with permission.)

Nonroutine Laboratory Workup

Plasma Insulin

There may be value in the addition of a fasting insulin measurement as a way to assess insulin resistance. Calculation of the “homeostasis model assessment (HOMA)” by the equation, fasting glucose (in mmol) ¥ fasting insulin (in μU/mL) ÷ 22.5, has been shown to be a reliable indicator of insulin resistance (Lansang et al., 2001). How-ever, for routine clinical practice, the identification of insulin resistance does not seem necessary.

Uric Acid

Hyperuricemia, frequently seen in untreated hypertensives, is an independent risk marker for subsequent cardiovascular disease (Verdecchia et al., 2000). Nonetheless, as with serum fibrinogen and homocysteine levels, measurement of serum uric acid is not recommended as part of the routine workup.

Plasma Renin Activity

For many years, Laragh and colleagues (Mueller and Laragh, 1991; Laragh, 2001) have emphasized the value of ascertaining the plasma renin level coupled with the

level of 24-hour urinary sodium excretion, the renin-sodium profile. In various guidelines by expert committees (e.g., Joint National Committee, 1997), this profile is not recommended as part of the routine evaluation of all hypertensives but rather as a diagnostic tool if other features of low-renin states (e.g., primary aldosteronism) or high-renin states (e.g., renovascular disease) are present.

Additional Testing for Target Organ Damage

Cardiac Assessment

All hypertensives should have electrocardiography. The recognition of LVH by electrocardiography using various documented criteria

identifies increased cardiovascular risk (Okin et al., 2000). Echocardiography, although it is much more sensitive in identifying LVH, is recommended only for those patients with an over-all low-risk status who meet current criteria for *not* starting antihypertensive therapy (de Simone et al., 2000b). Obviously, if LVH is present, therapy would be indicated. Echocardiography is not recommended for those whose overall risk status necessitates active drug therapy, as it does not appear to be a better guide to therapy than is the level of BP. However, the availability of low-cost, portable echocardiography devices that measure LV short-axis diameter and wall thickness may greatly expand the use of such limited echocardiography (Cohn, 2001).

Cerebral Assessment

Although sensitive testing may show that neurobehavioral function is reduced (Blumenthal et al., 1993), it is not possible to relate cerebral dysfunction to the severity of the BP, unless hypertension has become accelerated with resultant encephalopathy. In the presence of symptoms of cerebral ischemia, particularly transient ischemic attacks, the finding of a carotid bruit indicates the need for carotid ultrasonography in the hope of finding a correctable lesion. Asymptomatic hypertensives have been found to have more white-matter lesions by brain magnetic resonance imaging (Lindgren et al., 1994); also, vascular forms of dementia are seen more frequently in those with hypertension (Skoog et al., 1996).

Renal Assessment

The earliest renal symptom is nocturia, and the most commonly identifiable markers of renal involvement are hyperuricemia and microalbuminuria (Pedrinelli et al., 1997), which can progress, although rarely, to nephrotic-stage proteinuria (Innes et al., 1993). Later, serum creatinine begins to rise, but the relationship between loss of renal function and rise of serum creatinine is asymptotic; thus, little absolute increase in serum creatinine will occur until more than 50% of renal function is lost (Perrone et al., 1992).

Vascular Assessment

Hypertension is a risk factor for aortic aneurysm; thus, abdominal palpation should be performed, particularly in thin, elderly hypertensives with evidence of vascular disease elsewhere. Ultrasonography is needed for diagnostic certainty (van der Vliet and Boll, 1997). Peripheral vessels should be palpated for diminished pulse and auscultated for bruits.

Safar and associates have used a noninvasive procedure to measure radial artery wall thickness that is closely correlated to pulse pressure and LV mass (Mourad et al., 2000).

Arterial Compliance

Increasing awareness of the importance of pulsatile phenomena in the pathogenesis of cardiovascular damage has led to attempts to measure arterial compliance, a quantitative measure of the distensibility of the arterial system. Cohn (2001) and colleagues have developed a noninvasive measure of arterial compliance, the "oscillatory elasticity index," which may prove to be a valuable indicator of arterial properties.

Search for Identifiable Causes

The frequencies of various identifiable causes of hypertension shown in Table 1-7 are likely much too high for the larger population with mild, asymptomatic hypertension. Nonetheless, clues to the presence of an identifiable cause should be sought in the routine evaluation of every new hypertensive. If suggestive clues are found or if the patient has features of "inappropriate" hypertension (Table 4-10), additional workup for an identifiable cause should be performed.

Age of onset: <20 or >50 yr
Level of blood pressure: >180/110 mm Hg
Organ damage
Funduscopy grade II or beyond
Serum creatinine >1.5 mg/dL
Cardiomegaly or left ventricular hypertrophy as determined by electrocardiography
Presence of features indicative of secondary causes
Unprovoked hypokalemia
Abdominal bruit
Variable pressures with tachycardia, sweating, tremor
Family history of renal disease
Poor response to generally effective therapy

TABLE 4-10. *Features of "inappropriate" hypertension*

The studies listed in Table 4-11 as initial usu-ally will serve as adequate screening procedures. They are readily available to every practitioner. If they are abnormal, the listed additional proce-dures should be performed, along with whatever other tests are needed to confirm the diagnosis. More detail about these procedures is provided in their respective chapters.

Diagnosis	Diagnostic procedure	
	Initial	Additional
Chronic renal disease	Urinalysis; serum creatinine; renal sonography	Isotopic renogram; renal biopsy
Renovascular disease	Captopril-enhanced isotopic renogram; duplex sonography	Magnetic resonance or CT angiogram; aortogram
Coarctation	Blood pressure in legs	Echocardiogram; aortogram
Primary aldosteronism	Plasma and urinary potassium; plasma renin and aldosterone	Plasma or urinary aldosterone after saline load; adrenal CT scans and scintiscans
Cushing's syndrome	Morning plasma cortisol after 1 mg dexamethasone at bedtime	Urinary cortisol after variable doses of dexamethasone; adrenal CT scans and scintiscans
Pheochromocytoma	Plasma metanephrine; spot urine for metanephrine	Urinary catechols; plasma catechols (basal and after 0.3 mg/kg clonidine); adrenal CT scans and scintiscans

CT, computed tomography.

TABLE 4-11. *Overall guide to workup for identifiable causes of hypertension*

Need for Limitation

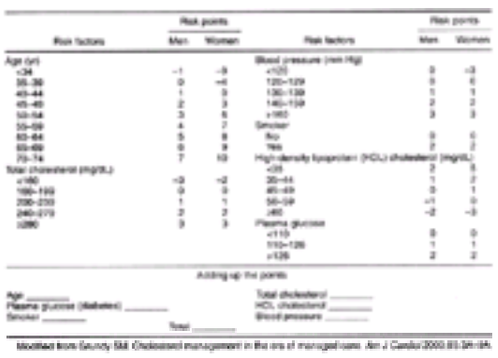
The various studies listed in Table 4-11 are not recommended for routine use, because an abnormal test result would more likely be a false-positive result in patients with a low likelihood of having one of these conditions (Diamond, 1999; McGinn et al., 2000). Only if suggestive clues are found in the initial routine workup should additional testing be done.

Assessment of Overall Cardiovascular Risk

Once the cause and consequences of the hypertension have been evaluated, it is necessary to assess the patient's overall cardiovascular risk status. The proper management of hypertension should involve attention to all of the risk factors that can be altered. Patients at high risk should be counseled and helped to reduce all of their risk factors. Because, for many patients, the BP is the easiest of the risks to control, this may be the first priority. As described more fully in the next chapter, the overall risk profile provides a more rational basis than an arbitrary BP level for determining whether and when to start treatment and the goal of therapy. For now, the need for a complete assessment of cardiovascular risk—a simple and inexpensive undertaking—should be obvious in the proper management of all hypertensives.

The Framingham Formula

Most assessments of cardiovascular risk focus on CHD, because that is the most common complication, and some use only “hard” events, excluding angina. Most assessments are based on data from the Framingham Heart Study, the longest and most complete follow-up of a carefully studied, large population (Kannel, 2000b). Most expert committees use their 10-year risk data,although models using shorter probabilities, either 2 years (D'Agostino et al., 2000) or 5 years (D'Agostino et al., 2001) may be more accurate. From a longer list of known risk factors, the Framingham data have used those shown in Table 4-12, which converts gradations in the various risk factors into points. These points then are used to establish the absolute 10-year risk (Table 4-13).



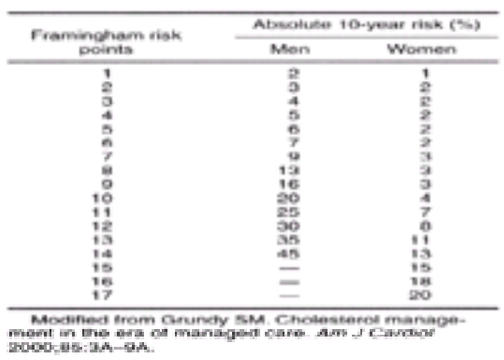
Risk factors	Risk points: Men	Risk points: Women	Risk factors	Risk points: Men	Risk points: Women
Age (yr)			Blood pressure (mm Hg)		
<34	−1	−9	<120	0	−3
35–39	0	−4	120–129	0	0
40–44	1	0	130–139	1	1
45–49	2	3	140–159	2	2
50–54	3	6	≥160	3	3
55–59	4	7	Smoker		
60–64	5	8	No	0	0
65–69	6	9	Yes	2	2
70–74	7	10	HDL-density lipoprotein (HDL) cholesterol (mg/dL)		
Total cholesterol (mg/dL)			≥60	1	2
<160	−3	−2	50–59	0	1
160–199	0	0	40–49	−1	0
200–239	1	1	<40	−2	−3
240–279	2	2	Plasma glucose		
≥280	3	3	<110	0	0
			110–126	1	1
			>126	2	2

Adding up the points

Age _____ Total cholesterol _____
Plasma glucose (diabetes) _____ HDL cholesterol _____
Smoker _____ Blood pressure _____
Total _____

Modified from Grundy SM. Cholesterol management in the era of managed care. Am J Cardiol 2000;85:9A–9A.

TABLE 4-12. *Scoring of risk factors used in the Framingham analyses*



Framingham risk points	Absolute 10-year risk (%) Men	Absolute 10-year risk (%) Women
1	2	1
2	3	2
3	4	2
4	5	2
5	6	2
6	7	3
7	9	3
8	13	3
9	16	3
10	20	4
11	25	7
12	30	8
13	35	11
14	45	13
15	—	15
16	—	18
17	—	20

Modified from Grundy SM. Cholesterol management in the era of managed care. Am J Cardiol 2000;85:9A–9A.

TABLE 4-13. *Absolute risk estimates for hard coronary heart disease according to Framingham points*

Although age overwhelms all else in increasing risk, the other factors are modifiable and therefore demand attention. Lest it be over-looked, an elevated BP serves as a major risk factor for cardiovascular disease even in the young (McCarron et al., 2000).

Other Formulas

A number of more detailed assessments of cardiovascular risks are available, including some that also estimate the risks for stroke, CHF, and peripheral vascular disease (Jackson, 2000) and others that are available as computer programs (Hingorani and Vallance, 1999).

All these risk estimates are based on data from large populations, among which only some individuals had hypertension. For hypertensives, therefore, an even more accurate assessment of the risk for cardiovascular death may be that derived from data obtained specifically from more than 47,000 hypertensive patients in 8 RCTs, of whom 1,639 died of cardiovascular diseases (Pocock et al., 2001).

A simpler division of overall risk was presented in the 1997 sixth report of the U.S. Joint National Committee (Joint National Committee, 1997). That stratification, although not as precise as is used in other major guidelines, has the advantage of also taking into account the presence of hypertension-related target organ dam-age and clinical cardiovascular disease. Because that risk stratification is used primarily as a guide to the need for institution of therapy and to the choice of therapy, it is presented in the next chapter, which addresses in more detail the rationale, guidelines, and goals of treatment.

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5
Treatment of Hypertension:Why, When, How Far

In the preceding four chapters, the epidemiology, natural history, and pathophysiology of primary (essential) hypertension were reviewed. We will now turn to its treatment, examining the benefits and costs of therapy in this chapter and the use of nondrug and drug treatment in the two chapters that follow.

In this chapter, three main questions are addressed:

- First, what is the evidence that treatment is beneficial?
- Second, at what level of blood pressure (BP) should active drug therapy be started? Lifestyle modifications, which will be examined in the next chapter, can be justified for everyone, hypertensive or not.
- Third, what is the goal of therapy and, further, are there different goals for different patients?

EVIDENCE FOR BENEFITS OF THERAPY

The evidence for benefits of therapy comes in part from epidemiologic and experimental evidence but mainly from the results of large-scale therapeutic trials.

Epidemiologic Evidence

Epidemiologic evidence, covered in Chapter 1, provides a clear conclusion: The risks of cardiovascular morbidity and mortality rise progressively with increasing BP levels (MacMahon et al., 1990).

Interrupting the Progress of Hypertension

The 15- to 17-year longitudinal study of Welshmen by Miall and Chinn (1973) and the 24-year follow-up of American aviators by Oberman et al. (1967) showed that hypertension begets further hypertension. In both studies, the higher the BP, the greater was the rate of change of pressure, pointing to an obvious conclusion: Progressive rises in BP can be prevented by keeping the pressure down. This conclusion is further supported by the results of the major placebo-controlled trials of antihypertensive therapy: Whereas 10% to 17% of those on placebo progressed beyond the threshold of diastolic pressure above 110 mm Hg, only a small handful of those on drug treatment did so (see Chapter 4).

Evidence from Natural Experiments in Humans

Vascular damage and the level of BP can be closely correlated in three situations: unilateral renal vascular disease, coarctation, and pulmonary hypertension. These three experiments of nature provide evidence that what is important is the level of the BP flowing through a vascular bed and not some other deleterious effect associated with systemic hypertension. Tissues with lower BP are protected; those with higher pressure are damaged.

- The kidney with renal artery stenosis is exposed to a lower pressure than is the contralateral kidney without stenosis. Arteriolar nephrosclerosis develops in the high-pressure nonstenotic kidney, occasionally to such a degree that hypertension can be relieved only by removal of the nonstenotic kidney, along with repair of the stenosis (Thal et al., 1963).
- The vessels exposed to the high pressure above the coarctation develop atherosclerosis to a much greater degree than do the vessels below the coarctation, where the pressure is low (Hollander et al., 1976).
- The low pressure within the pulmonary artery ordinarily protects these vessels from damage. When patients develop pulmonary hypertension secondary to mitral stenosis or certain types of congenital heart disease, both arteriosclerosis and arteriolar necrosis often develop within the pulmonary vessels (Heath and Edwards, 1958).

Evidence from Animal Experiments

Just as hypertension accelerates and worsens atherosclerosis in humans, animals that are made hypertensive develop more atherosclerosis than do normotensive animals fed the same high-cholesterol diet (Chobanian, 1990). In animals, the lesions caused by hypertension, including accelerated atherosclerosis, can be prevented by lowering the pressure with antihypertensive agents (Chobanian et al., 1992).

Evidence from Clinical Trials of Antihypertensive Therapy

The last piece of evidence—that there is benefit from lowering an elevated BP—is the most important. Over the last four decades, since oral antihypertensive therapy has become available, protection with antihypertensive therapy has been demonstrated at progressively lower levels of pressure and, more recently, in the elderly.

In the latest metaanalysis of all properly controlled trials, which includes 27 trials of 136,124 patients, Staessen et al. (2001) conclude:

> Our main finding was that results of outcome trials for antihypertensive drugs can be explained by blood pressure differences between randomised groups. All antihypertensive drugs had similar long-term efficacy and safety. Our results show the desirability of lowering blood pressure as much as possible to achieve the greatest reduction in cardiovascular complications.

As important as these data are, there are multiple problems in transposing the results of relatively short-term randomized, controlled trials (RCTs) into guidelines for

clinical practice. More about this will follow the presentation of the results of the trials.

Trials in Malignant Hypertension

The benefits of drug therapy in malignant hypertension were easy to demonstrate in view of its predictable, relatively brief, and almost uniformly fatal course in untreated patients. Starting in 1958, a number of studies appeared showing a significant effect of medical therapy in reducing mortality in malignant hypertension (see Chapter 8).

Trials in Less Severe Hypertension

Demonstrating that therapy made a difference in nonmalignant, primary hypertension took a great deal longer. However, during the late 1950s and early 1960s, reports began to appear that suggested that therapy of nonmalignant hypertension was helpful (Hodge et al., 1961; Hood et al., 1963; Leishman, 1961). The first controlled, albeit small, study by Hamilton et al. (1964) showed a marked decrease in complications over a 2- to 6-year interval for 26 effectively treated patients as compared to 31 untreated patients.

Veterans Administration Cooperative Study

The first definitive proof of the protection provided by antihypertensive therapy in nonmalignant hypertension came from the Veterans Administration Cooperative Study, begun in 1963. The value of therapy in the 73 men with diastolic BPs of 115 to 129 mm Hg given hydrochlorothiazide, reserpine, and hydralazine versus the 70 men given placebo became obvious after less than 1.5 years, with a reduction in deaths from 4 to 0 and in major complications from 23 to 2 [Veterans Administration Cooperative Study Group (VA), 1967].

Along with the men with diastolic BPs of 115 to 129 mm Hg, another 380 with diastolic BPs between 90 and 114 mm Hg also were assigned randomly to either placebo or active therapy. It took a longer time—up to 5.5 years, with an average of 3.3 years—to demonstrate a statistically clear advantage of therapy in this group (VA, 1970). A total of 19 of the placebo group but only 8 of the treated group died of hypertensive complications, and serious morbidity occurred more often among the placebo group. Overall, major complications occurred in 29% of the placebo group and 12% of the treated group.

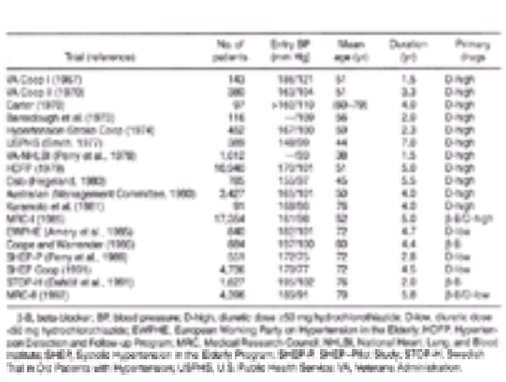
Additional Randomized, Controlled Trials

The promising results of the Veterans Administration study prompted the initiation of a number of additional controlled trials of therapy of hypertension.

As Collins and MacMahon (2001) have emphasized, RCTs are required to assess reliably the modest effects of treatment on major outcomes that are expected in patients with mild to moderate hypertension. Fortunately, many more have now been completed, and a number of metaanalyses have been performed on the data generated from the multiple RCTs performed over the last 30 years. The three metaanalyses that will be described are those of Psaty et al. (1997), which examined all the RCTs done prior to 1995; the Blood Pressure Lowering Treatment Trialists' Collaboration (Blood Pressure Lowering Trialists, 2000), which examined all the RCTs completed between 1995 and 2000; and Staessen et al. (2000), which examined RCTs in elderly patients with isolated systolic hypertension (ISH).

Trials before 1995

The 18 trials listed in Table 5-1 included a total of 48,220 patients followed up for an average of 5 years (Psaty et al., 1997). In all these trials, the primary drugs were either b-blockers or diuretics; those trials done before the mid-1980s almost all used higher doses of diuretic. It should be noted that the entry BP criterion for all of the trials before the Systolic Hypertension in the Elderly Program–Pilot Study (SHEP-P) in 1989 was the diastolic level, reflecting the greater emphasis placed, until recently, on diastolic rather than systolic BP as the major determinant of risk.



Trial (reference)	No. of patients	Entry BP (mm Hg)	Mean age (yr)	Duration (yr)	Primary drugs
VA Coop I (1967)	143	115/121	57	1.5	D-high
VA Coop II (1970)	380	103/104	57	3.3	D-high
Carter (1972)	97	>110/110	69–76	4.0	D-high
Barraclough et al. (1973)	116	—/109	56	2.0	D-high
Hypertension Stroke Coop (1974)	402	107/100	59	2.3	D-high
USPHS (Smith, 1977)	389	146/99	44	7.0	D-high
VA-NHLBI (Perry et al., 1979)	1,012	—/90	38	1.5	D-high
HDFP (1979)	10,940	170/101	51	5.0	D-high
Oslo (Hegland, 1983)	785	133/97	45	5.5	D-high
Australian (Management Committee, 1980)	3,427	163/101	50	4.0	D-high
Kuramoto et al. (1981)	91	158/99	75	4.0	D-high
MRC-I (1985)	17,354	161/96	52	5.0	β-B/D-high
EWPHE (Amery et al., 1985)	840	162/101	72	4.7	D-low
Coope and Warrender (1986)	884	167/100	60	4.4	β-B
SHEP-P (Perry et al., 1989)	551	170/75	72	2.8	D-low
SHEP Coop (1991)	4,736	170/77	72	4.5	D-low
STOP-H (Dahlöf et al., 1991)	1,627	195/100	76	2.0	β-B
MRC-II (1992)	4,396	165/91	70	5.8	β-B/D-low

β-B, beta-blocker; BP, blood pressure; D-high, diuretic dose ≥50 mg hydrochlorothiazide; D-low, diuretic dose <50 mg hydrochlorothiazide; EWPHE, European Working Party on Hypertension in the Elderly; HDFP, Hypertension Detection and Follow-up Program; MRC, Medical Research Council; NHLBI, National Heart, Lung, and Blood Institute; SHEP, Systolic Hypertension in the Elderly Program; SHEP-P, SHEP–Pilot Study; STOP-H, Swedish Trial in Old Patients with Hypertension; USPHS, U.S. Public Health Service; VA, Veterans Administration.

TABLE 5-1. *Randomized placebo-controlled trials of antihypertensive drug treatment published before 1995*

The trials published before 1985 mainly involved younger patients; those in the early 1990s enrolled elderly hypertensives with either combined hypertension or ISH, who will be examined separately.

Separation of the Data by Doses

Psaty et al. (1997) separated the nine trials that involved high doses of diuretic (equivalent to 50 mg or more of hydrochlorothiazide) from the four that involved lower doses (equivalent to 12.5 to 25.0 mg hydrochlorothiazide) and the four that used a b-blocker as the primary drug (Fig. 5-1). The Hypertension Detection and Follow-up Program study was considered separately, as it was not placebo controlled: Half of the patients were more intensively treated (stepped care); the other half were less intensively treated (referred care).

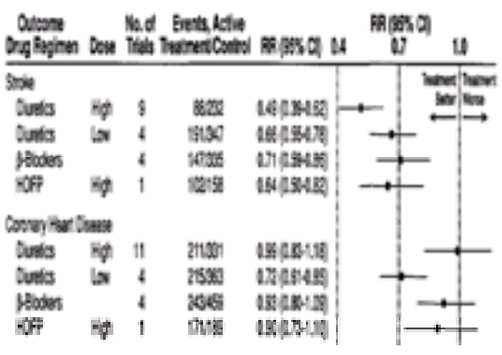


FIG. 5-1. Metaanalysis of randomized, placebo-controlled clinical trials in hypertension according to firstline treatment strategy. For these comparisons, the numbers of participants randomized to active therapy and placebo were 7,758 and 12,075 for high-dose diuretic therapy; 4,305 and 5,116 for low-dose diuretic therapy; and 6,736 and 12,147 for b-blocker therapy. HDFP, Hypertension Detection and Follow-up Program; RR, relative risk; CI, confidence interval. (Reprinted from Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as firstline agents. *JAMA* 1997;277:739–745, with permission.)

The separation of the data by doses clearly reveals the lack of protection from coronary heart disease (CHD) by high doses of diuretic and b-blockers, whereas all therapies had a significant impact on stroke. The authors concluded: “Diuretics and b-blockers—inexpensive antihypertensive agents—have been proven to be both safe and effective in large long-term randomized clinical trials. Recent studies have also given us a new appreciation for the importance of low-dose diuretic therapy for the prevention of coronary disease as well as stroke” (Psaty et al., 1997).

Conclusion

Based on these trials, primarily in middle-aged patients with combined systolic and diastolic hypertension, the evidence was clear: Reductions in BP of 10 to 12 mm Hg systolic and 5 to 6 mm Hg diastolic for a few years conferred relative reductions of 38% for stroke and 16% for CHD (Collins and MacMahon, 1994). The sizes of these reductions were consistent with those predicted from observational studies of the long-term relations between BP with risk of stroke and coronary disease (MacMahon et al., 1990). The relative reductions were similar in various subgroups of patients, seemingly independent of differences in the event rates in the placebo-treated controls.

Trials after 1995

After 1995, a new series of trials were completed and many more started to determine the effects of newer antihypertensive agents— angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, and calcium channel blockers (CCBs)—and to broaden the patient population to those with associated conditions including coronary disease, diabetes, and renal insufficiency.

Collaborative Overview

To reduce random error and bias and to ensure comparability between various trials, in July 1995 the principal investigators from all the large-scale trials then in progress or in advanced stages of planning agreed to collaborate on prospective overviews in which treatment effects would be estimated from the combined results of individual studies (World Health Organization, 1998). As will be described, separate overviews were planned for trials comparing active treatments against placebo, trials comparing more intensive with less intensive strategies (covered in the section Goal of Therapy, later in this chapter), and trials comparing different drug classes (covered in the first portion of Chapter 7).

Placebo-Controlled Trials

The first analysis of this collaborative overview was published in late 2000 (Blood Pressure Lowering Trialists, 2000). As originally designed, the trials that were included had to have a minimum of 1,000 patient-years of follow-up, regardless of whether the intent was to lower BP or whether the patients were selected on the basis of hypertension. As seen in Table 5-2, the average BP of the enrollees in the top five of the six trials was not elevated. In those five trials, the indication for entry was coronary or other cardiovascular disease or diabetes, and most of the enrollees were on a variety of other drugs in addition to the study drug (or placebo). Of these trials, only in the Systolic Hypertension in Europe (Syst-Eur) trial were enrollees chosen on the basis of hypertension—in this instance, ISH.

Trial (reference)	No. of patients	Entry blood pressure (mm Hg)	Mean age (yr)	Duration (yr)	Primary drugs
HOPE (Heart Outcomes, 2000a)	9,297	139/79	66	5	Ramipril
PART2 (MacMahon et al., 2000)	617	133/79	61	4	Ramipril
QUIET (Cashin-Hemphill et al., 2000)	1,750	133/74	58	2	Quinapril
SCAT (Teo et al., 2000)	460	130/78	61	5	Enalapril
PREVENT (Pitt et al., 2000)	825	126/76	57	3	Amlodipine
Syst-Eur (Staessen et al., 1997)	4,695	174/86	70	2	Nitrendipine

HOPE, Heart Outcomes Prevention Evaluation Study; PART2, Prevention of Atherosclerosis with Ramipril Trial; PREVENT, Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial; QUIET, Quinapril Ischaemia Event Trial; SCAT, Simvastatin/Enalapril Coronary Atherosclerosis Trial; Syst-Eur, Systolic Hypertension in Europe Trial.

TABLE 5-2. *Randomized placebo-controlled trials of antihypertensive drug treatment published from 1995 to 2000*

As was true for most of the pre-1995 trials shown in Table 5-1, approximately three-fourths of the patients remained on their assigned treatment at the end of follow-up, a mean of 3.8 years. The differences in BP between the drug and the placebo-treated groups in the top five trials were 3/1 mm Hg; in the Syst-Eur trial, the difference was 10/5 mm Hg. The status of more than 95% of the enrolled patients was known at the end of follow-up.

Angiotensin-Converting Enzyme Inhibitors versus Placebo

Figure 5-2 and Figure 5-3 show the results of the six placebo-controlled trials. To reiterate, all four studies comparing ACEIs with placebo (Fig. 5-2) involved patients with a history of cardiovascular disease or diabetes, not necessarily hypertension. In the Heart Outcomes Prevention Evaluation (HOPE) trial, which provided 90% of the data, 47% of the patients were hypertensive.

FIG. 5-2. Comparisons of angiotensin-converting enzyme inhibitor (ACE-I)–based therapy with placebo. Boxes and horizontal lines represent relative risk and 95% confidence interval (CI) for each trial. Size of boxes is proportional to inverse of variance of that trial result. Diamonds represent the 95% CI for pooled estimates of effect and are centered on pooled relative risk. HOPE, Heart Outcomes Prevention Evaluation study; NA, not available; PART2, Prevention of Atherosclerosis with Ramipril Trial; p homog, *p* value from c^2 test for homogeneity; QUIET, Quinapril Ischaemia Event Trial; SCAT, Simvastatin/Enalapril Coronary Atherosclerosis Trial. (Reprinted from Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000;356:1955–1964, with permission.)

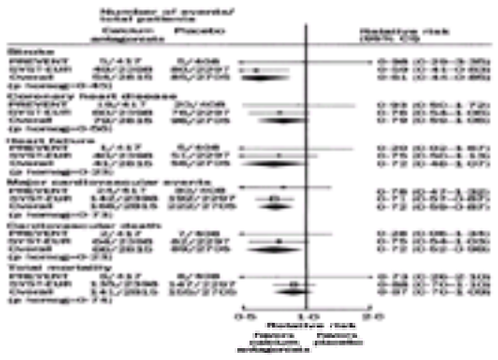


FIG. 5-3. Comparisons of calcium antagonist–based therapy with placebo. Boxes and horizontal lines represent relative risk and 95% confidence interval (CI) for each trial. Size of boxes is proportional to inverse of variance of that trial result. Diamonds represent the 95% CI for pooled estimates of effect and are centered on pooled relative risk. p homog, *p* value from c^2 test for homogeneity; PREVENT, Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial; SYST-EUR, Systolic Hypertension in Europe Trial. (Reprinted from Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000;356:1955–1964, with permission.)

As seen in Figure 5-2, among patients assigned to ACEI therapy, there were statistically significant (20–30%) reductions in stroke, coronary disease, major cardiovascular events, and mortality, whereas the reduction in the risk for heart failure was not significant. The failure to show a statistically significant reduction in heart failure likely reflects the small number of events and the widespread prehospital use of ACEIs in patients with congestive heart failure, as several other RCTs have documented the protection from heart failure by ACEIs (Flather et al., 2000). The benefits of the addition of ACEI to the other therapies in the HOPE trial were similar in those with or without hypertension.

Calcium Channel Blockers versus Placebo

In the two trials comparing CCB-based therapy to placebo (Fig. 5-3), 90% of the events were seen in the Syst-Eur trial of ISH. Among patients assigned to CCB therapy, there were significant (30–40%) reductions in stroke, major cardiovascular events, and mortality, whereas the reductions in the risk for CHD, heart failure, and total mortality were not statistically significant. The trialists note that "the estimates of treatment effect from this predominantly hypertensive population of patients largely preclude adverse effects of the magnitude suggested by earlier overviews of other trials of dihydropyridine agents (mainly shortacting nifedipine) among patients with acute myocardial infarction or unstable angina" (Blood Pressure Lowering Trialists, 2000).

Conclusions

These data document that the benefits of BP-lowering drugs are not limited to diuretic or b-blockerbased regimens. However, as the trialists (Blood Pressure Lowering Trialists, 2000) state:

> . . . [A]lthough the results of these prospectively planned overviews provide answers to some of the questions they were designed to address, uncertainty remains about others. There are some unresolved issues about the cause-specific effects of treatments compared with none, such as the persisting uncertainty about effects of calcium antagonists on CHD and heart failure in hypertensive patients and others. There are other unresolved issues about differences between active regimens in their cause-specific effects. . . . Resolution of many of these unresolved issues should be provided by results of ongoing or planned trials, and future rounds of analyses from this programme of prospectively designed overviews. Such analyses will eventually include data from at least 25 randomized trials [Table 5-3]. The results should increase the precision of estimates of cause-specific differences between the effects of more intensive and less intensive blood-pressure-lowering strategies and between the effects of regimens based on ACE inhibitors, calcium antagonists, and diuretics or b-blockers. The results should also provide new estimates of the effects of angiotensin II antagonists compared with other agents, as well as substantially increasing the evidence available about the effects of various blood-pressure-lowering drugs in important subgroups of patients, such as those with diabetes mellitus, renal disease, or cerebrovascular disease. In this way, the collaborative programme should continue to provide important evidence about the treatment regimens likely to provide the greatest benefits to patients in various different circumstances.

TABLE 5-3. *Ongoing trials potentially eligible for inclusion in future overviews (listed in order of projected completion date)*

Trials in the Elderly with Isolated Systolic Hypertension

Although both the earlier and the later trials listed in Tables 5-1 and 5-2 include some elderly patients with ISH, the fact that such patients make up the largest portion of hypertensive patients now and, to an even greater degree in the future, justifies a closer, separate look at the data on their therapy. Staessen et al. (2000) have provided a metaanalytyion of therapy. When Staessen et al. (2000) anasis of these trials, which are listed in Table 5-4.

Trial (reference)	No. of patients	Entry blood pressure (mm Hg)	Mean age (yr)	Duration (yr)	Primary drugs
EWPHE (Amery et al., 1985)	172	176/92	73	4.3	Diuretic
MRC-I (1985)	428	174/92	82	5.2	β-Blr/diuretic
Coope and Warrender (1987)	348	191/85	70	3.6	β-B
SHEP Coop (1991)	4,736	170/77	72	4.4	Diuretic
STOP-H (Dahlöf et al., 1991)	358	194/91	76	1.9	β-Blr/diuretic
MRC-II (1992)	2,857	182/83	70	6.1	β-Blr/diuretic
Syst-Eur (Staessen et al., 1997)	4,695	174/85	70	2.0	CCB
Syst-China (Liu et al., 1998)	2,394	170/86	67	3.0	CCB

β-B, beta-blocker; CCB, calcium channel blocker; EWPHE, European Working Party on Hypertension in the Elderly; MRC, Medical Research Council; SHEP, Systolic Hypertension in the Elderly Program; STOP-H, Swedish Trial in Old Patients with Hypertension; Syst-China, Systolic Hypertension in China trial; Syst-Eur, Systolic Hypertension in Europe trial.

[a]Diagnosis of systolic hypertension based on diastolic blood pressure below 95 mm Hg in all trials except SHEP, which required a diastolic blood pressure of <90 mm Hg.

TABLE 5-4. *Randomized placebo-controlled trials of antihypertensive drug treatment in elderly patients with isolated systemic hypertension*[a]

The only trial in Table 5-4 not included in Hypertension in China trial, no differences in the Table 5-1 or Table 5-2 is the Systolic Hypertension in China trial (Liu et al., 1998), because it was not randomized but rather used an alternating allocation of therapy. When Staessen et al. (2000) analyzed the results without the data from the Systolic Hypertension in China trial, no differences in the pooled estimates of relative benefit for stroke or coronary events but a small decrease for all-cause and

cardiovascular mortality were noted.

Figure 5-4 summarizes the data from all eight trials of the 15,693 elderly patients with ISH whose average BP at entry was 174/83 mm Hg and whose mean fall in BP over the median 3.8-year follow-up was 10.4/4.1 mm Hg. Therapy significantly reduced all-cause and cardiovascular mortality, 13% and 18% respectively, but had an even greater impact on morbidity: Coronary events were reduced by 23% and strokes by 30%. As is noted in the next section on those older than 80 years in these trials, mortality is unlikely to be reduced greatly by any intervention in the elderly. However, as long as mortality is not increased, the ability of antihypertensive therapy to reduce disabling morbidities in the elderly is certainly adequate justification for its wider application.

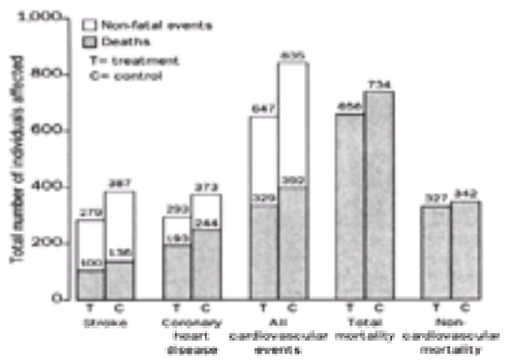


FIG. 5-4. Summarized results in 15,693 older patients with isolated systolic hypertension enrolled in eight trials of antihypertensive drug treatment. Blood pressure at entry averaged 174 mm Hg systolic and 83 mm Hg diastolic. During follow-up (median, 3.8 years), mean difference in blood pressure between treated and control patients was 10.4 mm Hg systolic and 4.1 mm Hg diastolic. (Reprinted from Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly. *Lancet* 2000;355:865–872, with permission.)

In these trials, the absolute benefits of active therapy were greater in men, older patients, and those with prior cardiovascular complications, reflecting the higher initial risk status of such patients. To prevent one major cardiovascular event, the numbers of patients that needed to be treated for 5 years were 18 men versus 38 women, 19 patients 79 years or older versus 39 patients 60 to 69 years old, and 16 of those with prior cardiovascular complications versus 37 of those without (Staessen et al., 2000).

Systolic versus Diastolic Pressure

In their analysis of the risks of either systolic or diastolic BP at study entry relative to the subsequent occurrence of morbidity or mortality in the placebo-treated controls in these multiple trials, Staessen et al. (2000) observed the expected positive correlation with systolic BP but a negative correlation with diastolic BP (Fig. 5-5). As noted in Chapter 4, the falling diastolic BP that typically is seen with aging reflects atherosclerotic rigidity of the large arteries, so the greater cardiovascular risk that accompanies lower diastolic BP comes as no surprise. The findings shown in Figure 5-5 highlight both the importance of the pulse pressure as the leading risk factor and the apparent increase in risk seen with further inadvertent lowering of already low diastolic BP when ISH is treated, an issue that is described at the end of this chapter in the section Goal of Therapy.

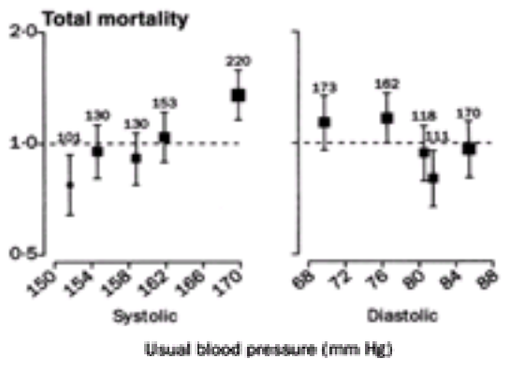


FIG. 5-5. Associations between relative risk for total mortality and usual blood pressure in 7,757 control patients. Solid squares represent risks in fifths of blood pressure distribution relative to common risk in all patients. Sizes of squares are proportional to number of events in each quintile. Vertical lines denote 95% confidence intervals. Relative risk adjusted for gender, age, and trial. Numbers on top are number of events per quintile. (Modified from Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly. *Lancet* 2000;355:865–872.)

Trials in the Very Old

Gueyffier et al. (1999) analyzed the data from all participants in seven RCTs who were 80 years and older, a total of 1,670 patients. These trials were the same as those in Table 5-4 with the exceptions of the two Medical Research Council trials and the addition of an open-label trial comparing two therapies that included 97 patients, the cardiovascular study in the elderly, or CASTEL study (Casiglia et al., 1994).

The analysis revealed 77 strokes and 28 stroke deaths in the 796 controls versus 57 strokes and 34 stroke deaths in the 874 drug-treated patients. Overall, treatment decreased strokes by 34%, major cardiovascular events by 22%, and heart failure by 39%, but there was no benefit for all-cause or cardiovascular mortality. The authors concluded:

> The inconclusive findings for mortality contrast with the benefit of treatment for nonfatal events. Results of a large-scale specific trial are needed for [a] definite conclusion that antihypertensive treatment is beneficial in very elderly hypertensive patients. Meanwhile, an age threshold beyond which hypertension should not be treated cannot be justified (Gueyffier et al., 1999).

Trials in Women

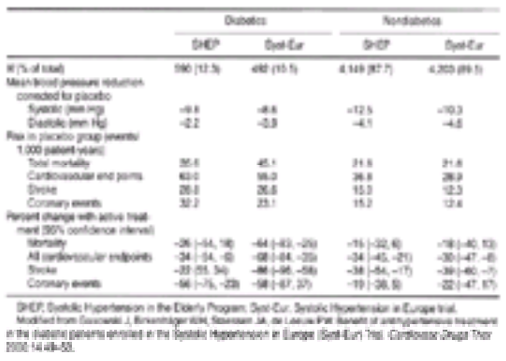
In the various previously described trials, women achieve less benefit from antihypertensive therapy than do men with similar levels of BP (Gueyffier et al., 1997). This reflects the lesser risk status for women than men, so that they achieve less absolute benefit. However, when women with equal degrees of risk as men are treated, they achieve virtually identical relative reductions in coronary disease and slightly greater protection against strokes (Gueyffier et al., 1997). This differential in overall risk can now easily be incorporated into the decision to start active drug therapy, as is described later in this chapter.

Trials in Diabetic Hypertensives

In view of the striking increase in obesity-related type 2 diabetes and the frequent coexistence of hypertension in such patients, attention will be given to the rather limited data from the diabetic hypertensives who composed 10% to 12% of the subjects enrolled in the previously described randomized placebo-controlled trials. The diabetics were analyzed separately in only two of these trials, the Systolic Hypertension in the Elderly Program (SHEP) (Curb et al., 1996) and the Syst-Eur trial (Tuomilehto et al., 1999). The data from the 3,577 diabetics enrolled in the HOPE trial (Heart Outcomes, 2000b) add to the considerable evidence that ACEIs provide additional benefit to diabetics at high risk, as they do for other high-risk patients. As is noted in Chapter 7 and Chapter 9, ACEIs appear to offer particular benefit in slowing the progression of diabetic nephropathy (Bakris et al., 2000), a benefit that has also been seen with angiotensin II-receptor blockers in patients with type 2

diabetes and microalbuminuria (Parving et al., 2001).

As seen in Table 5-5, in both the SHEP and Syst-Eur trials, approximately 500 diabetics were included in these two populations of elderly hypertensives with ISH. The patients were quite similar as reflected by the risks seen in the placebo-treated halves. In both trials, the diabetics did better than the nondiabetics except for a lesser reduction in strokes in the SHEP trial. Because the SHEP trial was based on a low dose of diuretic and the Syst-Eur trial on a dihydropyridine CCB, these positive effects suggest that any therapy that lowers BP will protect diabetics.



	Diabetics		Nondiabetics	
	SHEP	Syst-Eur	SHEP	Syst-Eur
N (% of total)	583 (12.3)	492 (10.1)	4,149 (87.7)	4,303 (89.1)
Mean blood pressure reduction, corrected for placebo				
Systolic (mm Hg)	−9.8	−8.6	−12.1	−10.3
Diastolic (mm Hg)	−2.2	−0.9	−4.1	−4.6
Rate in placebo group (events/1,000 patient-years)				
Total mortality	55.6	45.1	31.5	31.6
Cardiovascular end points	63.0	56.0	36.8	28.9
Stroke	20.0	26.6	10.3	12.3
Coronary events	32.2	23.1	15.2	12.4
Percent change with active treatment (95% confidence interval)				
Mortality	−26 (−54, 18)	−64 (−83, −25)	−15 (−32, 6)	−18 (−40, 13)
All cardiovascular endpoints	−34 (−54, −6)	−58 (−84, −23)	−34 (−45, −21)	−30 (−47, −8)
Stroke	−33 (−55, 34)	−66 (−96, −58)	−38 (−64, −17)	−39 (−66, −7)
Coronary events	−66 (−75, −23)	−58 (−67, 37)	−19 (−38, 5)	−22 (−47, 67)

SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe trial.
Modified from Staessen J, Birkenhäger WH, Bulpitt CJ, Fagard R, Leeuw PW. Benefit of antihypertensive treatment in the diabetic patients enrolled in the Systolic Hypertension in Europe (Syst-Eur) Trial. Cardiovasc Drugs Ther 2000;14:49–58.

TABLE 5-5. *Results of SHEP and Syst-Eur in diabetic and nondiabetic patients*

This conclusion receives additional support from the long-term follow-up of 3,642 type 2 diabetics who were in the original pool from which the 1,148 participants in the U.K. Prospective Diabetes Study were chosen (Adler et al., 2000). These patients, not enrolled in the formal trial, were followed up for a mean duration of 10.5 years by practitioners and presumably were given a wide mix of antihypertensive drugs. A strong association was noted between the risks for both macro- and microvascular complications and systolic BP with “no indication of a threshold for any of the complications below which risk no longer decreased” (Adler et al., 2000). There was a twofold lower incidence of risk from the median high (168 mm Hg) to the median low (114 mm Hg) level of systolic BP.

Trial Results and Clinical Practice

The sum total of the large number of randomized placebo-controlled trials in various types of hypertensive patients documents the value of active drug therapy (Staessen et al., 2001). The results of these RCTs have been the major force for progressively widening the web of active drug therapy to include both patients with lesser degrees of hypertension and those who are elderly. Yet there are factors that may either, on the one hand, exaggerate or, on the other, diminish the apparent benefits of therapy that are used to guide clinical practice.

Possible Underestimations of Benefit

Despite the previously noted significantly positive results of the multiple trials now available, these results may be an underestimate of the true benefits of antihypertensive therapy for a number of reasons, including the following.

Mislabeling of Patients

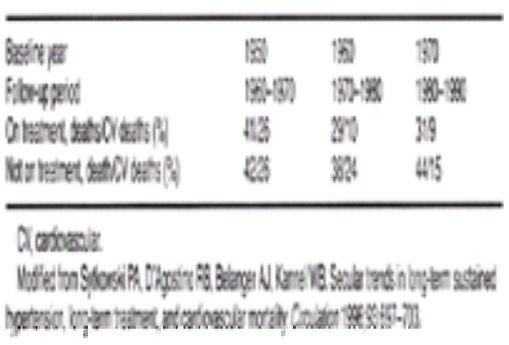
The ascertainment of hypertension for enrollment into the trials is usually based on two or three sets of officebased BP measurements over 1 to 2 months. As amply noted in Chapter 2, such limited measurements are likely to capture a large number of transient or isolated clinic (white-coat) hypertensives, thereby diminishing the efficacy of therapy, as all antihypertensive drugs lower BP more in relation to a higher starting BP, and most lower BP very little in the absence of persistent hypertension.

Intervention Too Late

Hypertension may produce damages well before patients have sufficiently high BP to be eligible for enrollment. Even if effectively treated, these damages may be irreversible, particularly if other risk factors are not also corrected.

Too Short Duration of Treatment

The duration of the trials is usually less than 5 years. However, the benefit of drugs may take much longer to become fully manifest, thereby minimizing the drugs' apparent efficacy. Table 5-6 shows data from the Framingham Heart Study that support a much greater efficacy of antihypertensive drug therapy over longer periods (Sytkowski et al., 1996). Successive cohorts of hypertensive patients aged 50 to 59 years were followed up for 20-year intervals, starting in 1950, 1960, and 1970. The evidence of cardiovascular disease was ascertained during the first 10 years of follow-up of each cohort, and mortality was assessed during the second 10 years. The percentages of all-cause mortality and cardiovascular mortality were similar in the 1950 cohort, whether or not the patients were receiving treatment for hypertension. However, both the 1960 and 1970 cohorts who were treated had significantly fewer deaths during follow-up than did the nontreated patients. Overall, the risk of all-cause mortality was reduced by 31% and the risk of cardiovascular mortality was reduced by 60% among those on long-term therapy.



Baseline year	1950	1960	1970
Follow-up period	1950–1970	1970–1986	1980–1986
On treatment, deaths/CV deaths (%)	41/25	29/10	3/1
Not on treatment, death/CV deaths (%)	42/26	38/24	44/15

CV, cardiovascular.
Modified from Sytkowski PA, D'Agostino RB, Belanger AJ, Kannel WB. Secular trends in long-term sustained hypertension, long-term treatment, and cardiovascular mortality. Circulation 1996;95:915–703.

TABLE 5-6. *Mortality among long-term, sustained hypertensive patients during the second 10 years of follow-up*

These results are much greater than those observed in the multiple short-term trials in the elderly shown in Figure 5-4. Therefore, the authors' conclusion that the long-term benefits of the treatment of hypertension may be much greater than those seen in shorter-term clinical trials seems appropriate.

The problem has been well framed by Zanchetti and Mancia (1996), who first agreed that short-term trials are suitable to assess the efficacy of therapy when “a relatively high rate of events is expected during the time span of the trial.” They go on to say:

> Using criteria derived from short-lasting eventbased trials for assessing the benefits and the costs of antihypertensive therapy in young and middle-aged subjects with mild hypertension quantitatively is, however, inappropriate. In these subjects the goal of antihypertensive therapy is not to prevent an unlikely hypertension-related event during the next 3–6 years, but rather to prevent or retard the development of cardiovascular lesions and help the subjects to attain their full life span. Because therapeutic trials lasting 20–30 years have never been performed, and are not likely to be performed, the possibility that calculations based upon actuarial life expectancy data may represent a more realistic far-sighted approach should be

discussed.

Inadequate Therapy

The approximately 12/6 mm Hg overall decreases in BP accomplished in the clinical trials are likely too little to reduce the damages of hypertension maximally. The degree of damage clearly relates to the level of BP achieved during therapy and not to the pretreatment level (Adler et al., 2000).

Because as many as 40% of patients in some trials did not reach the goal BP (Hansson et al., 1998), the benefits may then be less than what could have been obtained by more aggressive therapy.

Patients Lost to Follow-Up

In some trials, as many as 25% of patients are lost to follow-up before completion. In general, more high-risk patients are lost, weakening the evidence for benefit (Linjer and Hansson, 1997).

Switching of Patients

In all trials, a sizable number of patients initially randomized to placebo were switched to active therapy because their BP rose beyond the predetermined ceiling of presumed safety. As noted by Ramsay et al. (1996), “Treatment of these high-risk patients in the control groups will inevitably have reduced the cardiovascular disease event rates and led to underestimates of the absolute benefit in the intention-to-treat analyses which were, correctly, performed.”

Harm from Drugs

The drugs available and chosen for almost all the trials in subjects younger than 60 years old were high doses of diuretics and adrenergic inhibitors, mostly nonselective b-blockers. As is noted in Chapter 7, multiple metabolic abnormalities, which particularly aggravate lipid and glucose-insulin levels, have been amply documented with these therapies. As documented in Figure 5-1, these drug-induced abnormalities, particularly from high doses of diuretics, may have blunted or reversed the improvement in coronary risk provided by reduction of the BP. Protection against stroke, which is more directly related to BP and less affected by these other risk factors, would have been less influenced.

Noncompliance with Therapy

Patients assigned to active drug therapy may not have taken all of their medication and thereby would have had less benefit. Although pill counts are usually performed, no truly accurate assessment of compliance has been used.

Possible Overestimates of Benefit

On the other hand, in routine clinical practice, antihypertensive therapy may be less effective than is seen in controlled trials. In a 22-year follow-up of 686 hypertensive men who were provided “continuous good blood pressure control,” mortality increased steadily after the first 10 years in comparison to that seen in nonhypertensive men (Andersson et al., 1998). Such data may reflect many uncontrolled factors, but they suggest that data from clinical trials may overestimate the benefits of therapy as they are applied to the universe of hypertensives. Among the multiple factors that may overestimate the apparent benefits of therapy from clinical trial data are the following.

Exclusion of High-Risk Patients

In many prior RCTs, patients with various symptomatic cardiovascular diseases, target organ damage, or major risk factors were excluded, leaving a fairly healthy population who may respond better than the usual mix of patients. As noted in an earlier analysis of trials in the elderly, “patients with significant comorbidities and complicated medical regimens may also have poorer compliance, less overall benefit, and more adverse effects than trial participants” (Mulrow et al., 1994).

Better Compliance with Therapy

Patients enrolled in trials in which medications and all health care are free and follow-up is carefully monitored are likely to be more compliant with therapy than patients in clinical practice. Therefore, they may achieve greater benefit.

Coronary Disease versus Stroke

As seen in the results of all 25 clinical trials, greater protection has been observed against stroke than against coronary disease. In most populations, however, relatively more coronary disease than stroke is seen (Ramsay et al., 1996). Therefore, on a population-wide basis, less overall benefit may be provided by therapy than the data suggest.

Relative versus Absolute Changes

The reductions in CHD and stroke shown in Figure 5-1 Figure 5-1 and Figure 5-3 are relative—that is, they are the difference between the rates seen in treated versus untreated patients. However, as documented in Table 5-7, large relative differences may translate into small absolute differences. The presentation of trial data as large relative reductions in risk is much more attractive to the public and practitioners than the usually much smaller absolute reductions (Steiner, 1999); however, the relative data may easily mislead the unwary into thinking that many more patients will be helped than is possible.

Hypertension	Control group (C)	Active treatment group (A)	Relative risk reduction $[P_C - P_A)/P_C]$	Absolute risk reduction $(P_C - P_A)$	Number needed to treat $[1/(P_C - P_A)]$
Moderate (diastolic ≤115 mm Hg)					
Event rate (P)	0.20	0.12	0.40	0.08	13
Total no. of patients	15,778	16,866			
Mild (diastolic ≤110 mm Hg)					
Event rate (P)	0.015	0.009	0.40	0.006	167
Total no. of patients	15,165	15,238			

Modified from Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;310:452–454.

Based on the results of Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke and coronary heart disease: 2. Short-term reductions in blood pressure. *Lancet* 1990;335:827–838.

TABLE 5-7. *Calculations of relative and absolute risk reduction for patients with hypertension and number of patients needed to be treated to prevent one stroke in 5 years*

Cook and Sackett (1995) describe the issue thus:

> It is often clinically important to consider the baseline (control) risk of an event before recommending treatment since for a given relative risk reduction, the expected absolute benefit of treatment could vary considerably as the baseline risk changes. For example, an estimated relative risk reduction of 50% might be statistically significant and clinically important for patients at moderate to high risk of a particular adverse event. However, for patients with a low probability of an event the risk reduction might not be sufficient to warrant the toxicity and cost of active treatment. This is the main criticism of relative measures of treatment effect for the purposes of clinical decision making.

As shown in the far right column of Table 5-7, these investigators propose the use of the measure number needed to treat, calculated as the inverse of the absolute risk reduction, because it “conveys both statistical and clinical significance to the doctor” and “can be used to extrapolate published findings to a patient at an arbitrary specified baseline risk” (Cook and Sackett, 1995).

The need for using absolute risk, or number needed to treat, is well demonstrated in Figure 5-6 (Lever and Ramsay, 1995). Figure 5-6A shows the quite similar reductions in relative risk for stroke in six major trials in the elderly and in the earlier Medical Research Council trial of younger hypertensives. Figure 5-6B shows the same data in absolute terms, clearly portraying the progressively greater benefit of therapy with increasing pretherapy risk, as reflected in the rates in the placebo groups.

FIG. 5-6. Comparison of **(A)** proportionate (relative) and **(B)** absolute benefit from reduction in the incidence of stroke in six trials in the elderly and in one other [Medical Research Council I (MRC I)] having a similar design but in which the absolute stroke risk was much lower. Event rates are for fatal and nonfatal stroke combined. Aust, Australian study; EWPHE, European Working Party on High Blood Pressure in the Elderly trial; Coope, Coope and Warrender; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients with Hypertension. (Reprinted from Lever AF, Ramsay LE. Treatment of hypertension in the elderly. *J Hypertens* 1995;13:571–579, with permission.)

As will be noted, these absolute terms are needed when the trial results are used to make decisions about the value of therapy in patients at varying degrees of absolute risk.

Future Trials

As seen in Table 5-3, numerous large trials are now in progress or being planned. They will follow in large part the advice of Peto and Baigent (1998): “If one is trying to decide how millions of future patients should be treated, it may often be appropriate to randomize many thousands or even tens of thousands. . . . Generally the only practical way to achieve this is to design trials that are extremely simple and flexible; simplify the entry criteria, simplify the treatments, and simplify enormously the data requirements.”

The ongoing Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial is a good example of these principles and should provide evidence for moderate benefits of one or another form of therapy for the various types of hypertensive patients in the real world.

Other Data on the Benefits of Antihypertensive Therapy

In addition to the multiple controlled trials that examined the effects of therapy on CHD and stroke morbidity and mortality, many smaller studies have examined the influence of antihypertensive therapy on other end points, in particular left ventricular hypertrophy, carotid intimalmedial thickness, and proteinuria. Effects on such surrogate end points may be useful as guides to therapy and provide faster and less expensive ways to gain approval for new drugs. However, the recent controversy over drugs approved because they lowered BP without proof that they reduced mortality makes it unlikely that such surrogate end points will be used as evidence either for the overall benefits of therapy or for the selection of specific agents (Kaplan, 2001a).

Overall Mortality and Specific Causes of Death

Total mortality rates have fallen over the last 30 years, both for hypertensive and normotensive people in the United States and in most industrialized societies (see Chapter 1). Most of this fall is attributable to a decrease in deaths caused by cardiovascular diseases—stroke more than coronary disease.

However, the contribution made by antihypertensive therapy per se is uncertain. In the controlled trials, it seems likely that treatment is the major, if not exclusive, mechanism of reduction in death rates, with its predominant effect on stroke mortality. In the larger population, the control of hypertension is also credited for the fall in overall and coronary mortality (Kjellstrand et al., 1998). As shown in an analysis of the Framingham cohort in Table 5-6, improvements in the control of hypertension have contributed to the decline in mortality from cardiovascular disease over the last 30 years (Sytkowski et al., 1996).

Coronary Heart Disease

The treatment of hypertension may be at least partly responsible for the major shift in the causes of death among hypertensive patients over the last 30 years (see Chapter 4). Whereas congestive heart failure was responsible for more than half the deaths in hypertensive patients before 1950, its role diminished dramatically only to reappear as the population grew older (Alderman et al., 1998). At the same time, the proportion of deaths attributed to CHD have risen, likely reflecting, in part, the lesser impact of antihypertensive therapy on CHD mortality as compared to its greater impact on stroke.

Other Target Organs

Left ventricular hypertrophy has long been recognized as a major risk factor for cardiovascular mortality. Many studies have documented the ability of most antihypertensive drugs to effect regression of left ventricular hypertrophy. The effect may take years to document, and the impact on cardiovascular mortality is still uncertain (Devereux et al., 2001).

Renal damage can be delayed by antihypertensive therapy, although it may take much more intensive therapy with multiple drugs, including ACEIs (Bakris et al., 2000). The continuing rise in the incidence of end-stage renal disease in the United States (Joint National Committee, 1997) is largely attributable to the inclusion of more elderly and diabetic patients into the program of end-stage renal disease therapy.

Arterial structure and function have been improved by antihypertensive therapy (Schiffrin et al., 2000), but, here again, the translation of these improvements into clinical events has not been shown.

Overall Impact of Antihypertensive Therapy

As a last point, it should be noted that the analyses of the effect of antihypertensive therapy on the overall rates of cardiovascular disease in the population have shown that more extensive treatment and control of hypertension have had only a modest impact. Only 8% to 12% of the decline in coronary and stroke mortality over the last 15 years can be attributed to improved control of hypertension (see Chapter 1). Part of this arises from the fact that much of the populationwide risk for stroke and coronary disease is with people whose BPs are not “hypertensive” and, therefore, not currently considered in need of active (i.e., drug) therapy. More than half of excess deaths from CHD in the men screened for the Multiple Risk Factor Intervention Trial occurred in those with an initial systolic BP below 140 mm Hg (Julius,

2000).

Even if antihypertensive drug therapy could completely remove all the risks associated with definite hypertension, cardiovascular diseases would remain rampant in our high-risk population of smoking, sedentary, dyslipidemic, obese people. Only by reducing all these risks could meaningful prolongation of life expectancy be achieved (Smith et al., 2000).

Cost-Effectiveness of Treating Hypertension

Despite this rather pessimistic view, the treatment of hypertension is among the most costeffective measures now available for preventing avoidable death (Hodgson and Cai, 2001; Kjellstrand et al., 1998). The effects are quantitated as the cost of adding quality-adjusted life years. The figures in Table 5-8 are for England in mid-1990 and may differ in exact amounts from those in the United States, but the relative positions should be comparable (Maynard, 1992).

Maneuver	Cost ($), 1990
Cholesterol testing and diet therapy (all ages 40–69 yr)	409
Advice to stop smoking	502
Antihypertensive therapy to prevent stroke (ages 45–65 yr)	1,748
Pacemaker implantation for heart block	2,046
Cholesterol testing and drug treatment	2,753
Coronary bypass surgery, severe left main vessel disease with angina	3,887
Kidney transplant	8,761
Coronary bypass surgery, one-vessel disease, moderate angina	35,024
Hospital hemodialysis	40,864

Modified from Maynard A. The economics of hypertension control. *J Hum Hypertens* 1992;6:417–420.

TABLE 5-8. *Estimates of the costs of adding 1 quality-adjusted life-year*

The relatively crude data, however, do not address the true cost-effectiveness of antihypertensive therapy, an issue of increasing concern as the costs of health care have assumed increasing importance and as the treatment of hypertension has expanded. Swedish economist Johannesson (1995) has analyzed the cost-effectiveness of therapy for different patient groups in Sweden, using the net costs (treatment costs minus cost savings achieved through reduced cardiovascular morbidity) divided by the number of life-years gained. He used the Framingham data for the estimates of risk, including all of the pertinent risk factors described in Chapter 4 and the 1990 analysis by Collins et al. (1990) of the benefits of therapy, a 38% reduction in stroke, and a 16% reduction in CHD. The annual costs of therapy are based on those in Sweden in 1992, averaging nearly $300 for drugs (diuretics and b-blockers) and $200 for physician visits. In addition, the increased health care costs created by increased survival and the difference between consumption and production during the life-years gained were included (Johannesson et al., 1997). Because the years gained by a younger person will reduce costs by added productivity but those gained by an older person will increase costs by increased consumption, the calculations conclude that “it is generally cost-effective to treat middle-aged and older men and women in Sweden whose diastolic blood pressures are ³90 mm Hg, but that it is not generally cost-effective to treat younger men and women with mild hypertension” (Johannesson et al., 1997).

The most obvious problem with these data is their reliance on the relatively short-term results of the controlled trial data as the basis for benefits of therapy. Clearly, younger patients may require much longer periods of therapy to demonstrate benefit, but eventually their benefit may be even greater. As shown in Table 5-9, Zanchetti and Mancia (1996) have suggested that a more realistic way to consider costs is to use Metropolitan Life Insurance Co. actuarial data based on differences in life expectancy between normotensive and hypertensive subjects in the period between 1935 and 1954, before effective antihypertensive therapy was available. Assuming that therapy can reverse all hypertension-attributable stroke mortality and 50% of coronary mortality, they come up with a much lower cost-efficacy set of figures than do Johannesson et al. (1997).

Age (yr)	Normal life expectancy (yr)	Reduced life expectancy (yr)	Expected benefits (years of life)	Costs of treatment (U.S. dollars)	Cost/yr life gained (U.S. dollars)
35	41.5	9.0	5.4	21,500	4,000
45	32.0	6.0	3.6	16,700	4,650
55	23.5	4.0	2.4	12,400	5,200

*The reduced life expectancy is based on the differences between normotensive and hypertensive people in the years 1935–1954 from the Metropolitan Life Insurance Co. Actuarial data; the expected benefit is based on the assumption of complete reversibility of hypertension-attributable mortality from stroke and 50% from coronary disease and a coronary-stroke ratio of 4:1.

Modified from Zanchetti A, Mancia G. Benefits and cost-effectiveness of antihypertensive therapy. The actuarial versus the intervention trial approach. *J Hypertens* 1996;14:809–811.

TABLE 5-9. *Costs of therapy per year of life gained in men with a blood pressure of 140/95 mm Hg, based on actuarial life expectancy data*

The issue is not settled and, in the absence of data about widely used newer and more expensive drugs and the costs and benefits of long-term therapy, will likely never be settled (Pardell et al., 2000). The most cost-effective therapy may be one that allows the patient to die immediately (Bonneux et al., 1998), but we must always keep the appropriate long-term goal in mind.

Potential Constraints on Treatment of Hypertension

The issues of cost-effectiveness may seem remote and almost irrelevant to those who care for hypertensive patients. However, there are two reasons for everyone to pay attention to such issues. First, there are unintended risks of continued growth of medical care under the assumption that more is better (Fisher and Welch, 1999). Second, financial constraints are being imposed everywhere on health care, so that the decision to treat hypertension may need to be based on cost-effectiveness.

On the surface, the United States seems to be the exception, as health care spending will soon reach $2.2 trillion and, if current trends continue, will consume 25% of the gross national product by the year 2030 (Blumenthal, 2001). Even in the United States, however, the need to constrain the growth of the major federally financed program Medicare is being recognized, particularly with the rapid growth in the number of people older than 65. And, although the political will to provide universal health care coverage is not likely to develop in the near future, attention must be paid to the 45 million people in the United States who have no health insurance.

As these constraints increase, a collision may occur between the inherent desire to expand the number of hypertensive people under treatment and the societal need to limit health care expenditures. The late John Swales (2000), who served in the United Kingdom government for 3 years, wrote of this issue thus:

> The success of science has created painful dilemmas for health care across the world, whether funded through taxation or private insurance. A gap is opening up between aspiration and affordability. The treatment of hypertension provides an illuminating example of the problems this creates for clinical practice. These lead inevitably to social and political issues.
>
> The continuous gradient of risk associated with blood pressure implies that the benefits of reversing that risk will also be continuous. The lower the blood pressure level at which treatment is recommended, the smaller the probability of the individual benefiting and the greater the number of patients eligible for treatment. There is a continuous, inverse relationship between individual benefit and the total cost of health care. At some point a decision has to be made that the cost of treating a low level of risk is not justified. . . . The final decision concerning treatment clearly cannot be independent of the resources made available for treatment either by governments or private healthcare funders.
>
> Treatment of a hypertensive patient has to take place in the real world of constrained healthcare systems. . . . Excluding the social dimension can lead to serious errors and can weaken the case for more resources to be put into treating disorders such as hypertension. The cost of treating a large proportion of the population may be high, but the cost of not treating hypertension in terms of both hospital and social care is also high. The combined hospital and social care costs of treating stroke in England is 4 times the cost of managing hypertension,

> and there is actually a net return to society as a result of treating elderly hypertensives in terms of reduced indirect healthcare costs.

Constraints on the treatment of hypertension should be fairly easily resisted, because such treatment has been shown to be beneficial at costs that are low in comparison to most other therapies. As the demand for evidence-based medicine has grown, the treatment of hypertension stands as one of the prime examples wherein conclusive evidence is available. At the same time, the critical decision as to when to institute therapy has been more rationally defined in multiple guidelines, which will now be examined and which, hopefully, will be adopted into clinical practice.

WHEN SHOULD DRUG THERAPY BE STARTED?

Before addressing the question, “When should drug therapy be started?” one caveat must always be recalled: An initially elevated BP, above 140 mm Hg systolic or 90 mm Hg diastolic, must always be remeasured at least three times over at least 4 weeks to ensure that hypertension is present. Only if the level is very high (>180/110 mm Hg) or if symptomatic target organ damage is present should therapy be begun before the diagnosis is carefully established.

On the other hand, in view of the risks of even “high-normal” BP (Vasan et al., 2001), therapy in the future may be indicated for many more patients.

Problems with Past Guidelines

In the past, guidelines for the institution of therapy have been based solely on the level of BP, giving rise to major irrationalities and inconsistencies. As noted by Jackson et al. (1993),

> This has led to the situation in which a 60 year old woman with a diastolic BP of 100 mm Hg but no other risk factors (her absolute risk of cardiovascular disease is about 10% in 10 years) may meet the criteria for treatment, whereas a 70 year old man with multiple risk factors but a diastolic BP of 95 mm Hg (his absolute risk is about 50% in 10 years) may not.

On the basis of the results of the multiple clinical trials wherein reductions of BP by approximately 10/5 mm Hg resulted in reductions of overall cardiovascular risk by about one-third, the treatment of these two patients would be expected to reduce the absolute risk in the 60-year-old woman by nearly 3% in 10 years (30% of 10%) but in the 70-year-old man by approximately 17% (30% of 50%). As Jackson et al. (1993) note,

> In other words, if 100 women aged 60 with diastolic BP of 100 mm Hg and no other risk factors were treated for 10 years, about 3 events would be prevented, whereas if 100 men aged 70 with a diastolic BP of 95 mm Hg and multiple other risk factors were treated, about 17 events would be prevented.

Guidelines Using Overall Risk

The situation has recently changed dramatically for the better with widespread acceptance of targeting treatment not based arbitrarily on certain levels of BP but rationally on absolute cardiovascular risk (Baker et al., 2000). The change has been spurred on by numerous factors, including these:

- The long-time advocacy of risk-based guidelines by Alderman (1977), Alderman (1996), Freis (1982), Simpson (1990), and others.
- The increasingly loud call for evidence-based medicine as the basis for making decisions about the care of individual patients (Jackson and Sackett, 1996).
- The recognition that blind adherence to levels of BP as the criterion for therapy provides many patients no benefit and may actually increase their risk (Hoes et al., 1995).
- The presentation of a relatively simple, easily used nomogram that translates the concept into a practical method (Core Service Committee, 1995; Jackson, 2000; Jackson et al., 1993); increasingly, computers will be used to make the individual patient's overall risk assessment and provide guidance on therapeutic choices.

The New Zealand Recommendations

The New Zealand guidelines recommend that drug therapy be given for those with BP between 150/90 and 170/100 mm Hg if the predicted absolute 5-year risk of cardiovascular disease was 10% or higher from the Framingham data based on age, gender, levels of BP, ratio of total high-density lipoprotein cholesterol, smoking status, and presence of diabetes. The degree of risk can be easily determined from their graphs, the one for men shown in Figure 5-7. The benefits of lowering BP by the usual 10 to 15 mm Hg systolic and 5 to 8 mm Hg diastolic has been shown for the various risk levels (Table 5-10). The wisdom of using the 5-year risk of at least 10% rather than higher levels of risk was confirmed in a modeling study of hypertensives in Auckland, New Zealand (Baker et al., 2000). As expected, fewer patients would be given treatment at 15% or 20% risk levels, but many fewer cardiovascular events would be prevented.

5-Year cardiovascular risk level (based on Framingham Heart Study) (%)	Cardiovascular events prevented/100 treated for 5 yr[a]	No. needed to treat for 5 yr to prevent one event[a]
>30	>10	<10
25–30	9	11
20–25	7.5	13
15–20	6	16
10–15	5	25
5–10	2.5	40
2.5–5.0	1.25	80
<2.5	<0.8	>120

[a]Based on a reduction of 10 to 15 mm Hg systolic or 5 to 8 mm Hg diastolic.
Modified from Jackson R. Updated New Zealand cardiovascular disease risk-benefit prediction guide. *BMJ* 2000;320:710.

TABLE 5-10. *Expected benefits of treatment at different risk levels*

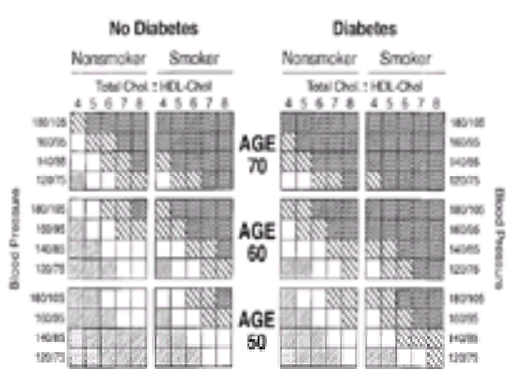


FIG. 5-7. Risk levels for men at varying ages and levels of blood pressure according to presence or absence of diabetes, smoking, and various levels of the ratio between total and high-density lipoprotein (HDL) cholesterol (chol). Risk of cardiovascular event in 5 years shown by stippled squares, 2.5% to 5.0%; closely hatched squares, 5% to 10%; open squares, 10% to 15%; widely hatched squares, 15% to 20%; and medium hatched squares, >20%. (Reprinted from Core Service Committee. *Guidelines for the management of mildly raised blood pressure in New Zealand*. Wellington, New Zealand: National Health Committee, 1995, with permission.)

Other Guidelines from Expert Committees

The guidelines from four expert committees published since 1997 have based the decision to start active drug therapy in those with BP of less than 160/100 mm Hg on the degree of overall cardiovascular risk. The British guidelines (Ramsay et al., 1999) use a coronary risk prediction chart similar to the one from New Zealand. The others use a more general approximation of risk (Feldman et al., 1999; Guidelines Subcommittee, 1999; Joint National Committee, 1997).

Table 5-11 lists the BP thresholds for institution of drug therapy in the various guidelines for four broad categories of risk. As seen, greater uniformity exists than in prior guidelines, but there are differences; as before, the United States is more liberal, the British more conservative. Hopefully, as the ability to determine cardiovascular risk becomes more reliable and accessible, all recommendations for initiation of therapy will be based on a quantitative assessment of risk. There will continue to be differences of interpretation and, even more so, differences in resources with which to implement guidelines.

	Blood pressure thresholds (mm Hg)			
Level of risk	United States (JNC, 1997)	WHO-ISH (Guidelines Subcommittee, 1999)	British (Ramsay et al., 1999)	Canadian (Feldman et al., 1999)
No target organ damage or risk factors	≥140/90	≥150/95	≥160*/100	≥160/100
With risk factors	≥140/90	≥140/90	≥160*/100	≥160/90
With target organ damage	≥130/85	≥140/90	≥140/90	≥160/90
With diabetes or renal insufficiency	≥130/85	≥130/85	≥140/90	≥140/90

JNC, Joint National Committee (on Detection, Evaluation, and Treatment of High Blood Pressure); WHO-ISH, World Health Organization–International Society of Hypertension.

TABLE 5-11. *Thresholds for institution of drug therapy in current guidelines*

The 1997 Sixth Joint National Committee Report

The recommendations made by the 1997 U.S. Joint National Committee (JNC-6) will be described, partly because of a pride of authorship but also because they have held up well as an accurate way to determine the long-term absolute benefit of therapy (Ogden et al., 2000).

JNC-6 gave attention to the overall risk status as well as the levels of BP in deciding on the need for drug therapy. The components for assessment of risk listed in Table 5-12 include major risk factors and evidence of target organ damage or clinical cardiovascular disease. As shown in Table 5-13, these are used to stratify patients with various levels of BP into three risk groups (JNC, 1997):

Major risk factors
Smoking
Dyslipidemia
Diabetes mellitus
Age >60 yr
Gender (men and postmenopausal women)
Family history of cardiovascular disease: women <65 yr or men <55 yr
Target organ damage and clinical cardiovascular disease
Heart diseases
Left ventricular hypertrophy
Angina or prior myocardial infarction
Prior coronary revascularization
Heart failure
Stroke or transient ischemic attack
Nephropathy
Peripheral arterial disease
Retinopathy

Modified from Joint National Committee. Sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 1997;157:2413–2446.

TABLE 5-12. *Components for cardiovascular risk stratification in patients with hypertension*

Characteristic	Risk group A	Risk group B	Risk group C
Major risk factors	Absent	Present	Absent or present
Target organ damage or clinical cardiovascular disease	Absent	Absent	Present
Blood pressure and stages (mm Hg)			
130–139/85–89 (high-normal)	Lifestyle modification	Lifestyle modification	Drug therapy[c]
140–159/90–99 (stage 1)	Lifestyle modification (up to 12 months)	Lifestyle modification[b] (up to 6 months)	Drug therapy
≥160/100 (stages 2 and 3)	Drug therapy	Drug therapy	Drug therapy

[a]Lifestyle modification should be adjunctive therapy for all patients recommended for pharmacologic therapy.
[b]For those with heart failure, renal failure, or diabetes.
[c]For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus lifestyle modifications.
Modified from Joint National Committee. Sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 1997;157:2413–2446.

TABLE 5-13. *Risk stratification and treatment*[a]

Risk group A includes patients with high-normal blood pressure or stage 1 hypertension who do not have clinical cardiovascular disease, target organ damage, or other risk factors. Persons with stage 1 hypertension are candidates for a longer trial (up to 1 year) of vigorous life-style changes with vigilant blood pressure monitoring. If goal blood pressure is not achieved, pharmacologic therapy should be added.

Risk group B includes patients with hypertension who do not have clinical cardiovascular disease or target organ damage but have one or more of the risk factors shown in [Table 5-12], but not diabetes mellitus. This group contains the large majority of patients with high blood pressure. If multiple risk factors are present, clinicians should consider antihypertensive drugs as initial therapy. Lifestyle modifications and management of reversible risk factors should be strongly recommended.

Risk group C includes all patients with hypertension who have clinically manifest cardiovascular disease as delineated in [Table 5-12]. . . .Some patients who have high-normal blood pressure as well as renal insufficiency, heart failure, or diabetes mellitus should be considered for prompt pharmacological therapy. Lifestyle modifications always should be recommended appropriately as adjunct treatment.

In clinical practice, most hypertensives will be in groups B and C, largely because of age, gender, and the higher prevalence of dyslipidemia. Among the 2,794 subjects in the Framingham cohort who were examined between 1990 and 1995 and found to have high-normal BP (130–139 mm Hg/85–89 mm Hg) or hypertension, the relative frequencies of the three risk groups were as follows: group A, 2.4%; group B, 59.3%; group C, 38.2% (Lloyd-Jones et al., 1999). Overall, 39.4% qualified for lifestyle modification as their initial intervention according to the JNC-6 guidelines, whereas 60.6% would receive drug therapy, including almost one-third of those with high-normal BP. Similarly, among 324 Israeli hypertensives, fewer than 5% were classified as group A (Stern et al., 2000).

Should the Threshold Be Lower?

As seen in Table 5-13, JNC-6 recommends antihypertensive drug therapy for patients with BP below the traditional definition of hypertension if they have a high overall risk status. In other portions of this book, arguments have been made for a conservative approach to the use of active drug therapy for “mild,” low-risk

hypertensives. These concerns were delineated by Rose (1981), who wrote:

> In reality the care of the symptomless hypertensive person is preventive medicine, not therapeutics. . . . If a preventive measure exposes many people to a small risk, then the harm it does may readily outweigh the benefits, since these are received by relatively few. . . . We may thus be unable to identify that small level of harm to individuals from long-term intervention that would be sufficient to make that line of prevention unprofitable or even harmful. Consequently we cannot accept long-term mass preventive medication.

Rose's comment was written at a time when adverse effects of antihypertensive drugs were fairly common and their ancillary benefits, as on endothelial function and arterial structure, had not been recognized. As easier to take and more effective drugs have become available, some have argued that they be given to people who are not yet hypertensive in an attempt to prevent both the onset of elevated BP and the vascular damage that may develop before the level goes beyond the 140/90 mm Hg threshold.

Stevo Julius (2000) in particular has argued that drug therapy should be started earlier despite the lack of evidence of benefit, a lack that is attributable to the absence of long-term trials in subjects with BP below 140/90 mm Hg. To provide such evidence, a trial was begun in 1999 using an angiotensin II receptor blocker in half of patients whose BP is between 130 and 139 mm Hg systolic and 85 and 89 mm Hg diastolic (i.e., high-normal BP) (Julius, 2000).

In support of this position is evidence from the Framingham study that those with such high-normal readings have a significantly increased risk of cardiovascular disease, 2.5 times higher in women and 1.6 times higher in men, compared to those with optimal BP (Vasan et al., 2001).

Additional aspects of Julius's argument include the unproved and unlikely ability of lifestyle modifications alone to prevent hypertension and the demonstration in spontaneously hypertensive rats that the use of ACEIs before the appearance of hypertension will markedly attenuate if not completely block the expected rise in BP (Harrap et al., 1990; Wu and Berecek, 1993).

Overall Management

The bottom line is this: The majority of hypertensives has fairly mild, asymptomatic hypertension, and the benefits of treatment—measured as the reduction in complications—progressively decline the milder the degree of hypertension. Many patients receive relatively little benefit yet are exposed both to adverse side effects and to the fairly large financial costs of therapy. Therefore, for maximal patient benefit, a management strategy based on overall risk is rational and appropriate. The situation would obviously change if and when the earlier use of antihypertensive drug therapy is shown to prevent the progression of BP and cardiovascular damage in those with BPs lower than the currently accepted lower threshold for institution of therapy.

Now that the rationale for the institution of therapy has been described, let us turn to the issue of how far to lower the pressure.

GOAL OF THERAPY

Until recently, the general attitude was “the lower, the better.” However, a number of factors have led to a more cautious approach, including the following:

- The progressively lower threshold for instituting therapy, previously as high as 160/110 mm Hg, now as low as 130/85 mm Hg for some patients
- The inclusion of elderly patients with ISH and, obviously, low diastolic BP and the recognition that very low diastolic BP is associated with increased risk (Staessen et al., 2000)(Fig. 5-5)
- Perhaps most important, concerns over the possible existence of a J-curve for diastolic BP (i.e., a reduction in risk as diastolic BP is lowered down to some critical level but then increased risk as the pressure is lowered further)

Evidence for a J-Curve of Diastolic Pressure

An association between reduction of BP and ischemic injury was first suggested by Stewart (1979), who reported a fivefold increase in myocardial infarction among patients whose diastolic BP was reduced to less than 90 mm Hg. Stewart's report was largely neglected, but when Cruickshank et al. (1987) reported the same phenomenon, interest focused on the problem and has intensified progressively.

A number of long-term studies in patients with diastolic hypertension have evaluated the incidence of cardiovascular complications according to the mean instudy diastolic BP. Rather than demonstrating a progressive benefit at lower pressures, many of these trials have shown a J-curve in which the risk of cardiac events declines as the diastolic pressure falls from more than 100 mm Hg to 85 mm Hg but then rises back up at diastolic pressures below 80 to 85 mg Hg (Farnett et al., 1991; Samuelsson et al., 1990).

Cruickshank (2000) postulates that the probable mechanism for the increase in coronary ischemia with treatment-induced falls in diastolic pressure is an inability to maintain coronary blood flow as perfusion pressure falls because of impairment of autoregulation within atherosclerotic vessels (i.e., a fall in coronary flow reserve). As Strandgaard and Haunsø (1987) have demonstrated, the coronary circulation has poor autoregulatory reserve; because oxygen extraction is nearly maximal at rest, lowering the perfusion pressure can lead to myocardial ischemia. The problem is compounded in the presence of myocardial hypertrophy (Polese et al., 1991).

As noted in Chapter 2, falls in BP during sleep may be profound and further accentuated by inadvertent overtreatment. Mansour et al. (1993) have shown that hypertensives with left ventricular hypertrophy experience nocturnal ischemia in association with treatment-induced falls in diastolic pressure.

Evidence against a J-Curve of Diastolic Pressure

Cruickshank's presentation and concept have not gone unchallenged. In particular, questions have been raised as to the exactness of the critical level at which the break in the curve appears and the relatively few events that make up the curves (Hansson, 2000). Moreover, a decrease in coronary events has been seen in patients with left ventricular dysfunction whose initially low pressures were reduced even further by ACEI therapy, well below the break of 85 to 90 mm Hg in the J-curve (Yusuf et al., 1992). For these reasons, Fletcher and Bulpitt (1992), in their review of the available evidence, concluded that “the J-curve is probably a consequence, not a cause of coronary heart disease.”

Increased cardiovascular mortality also has been reported among nontreated persons whose natural diastolic BP is lower than 80 mm Hg. This was reported in an analysis of the original Framingham data by Anderson (1978) and among early hypertensives who served as controls in the trials of Coope and Warrender (1986) and the European Working Party on High Blood Pressure in the Elderly Trial (Staessen et al., 1989). Such increased mortality could reflect the presence of severe cardiac dysfunction unrelated to antihypertensive therapy. Thus, in the Framingham cohort, higher mortality rates at low diastolic BPs were seen in survivors of myocardial infarction but not in low-risk subjects (D'Agostino et al., 1991).

Two additional sets of data from patients who had preexisting cardiovascular disease suggest that the lower the BP the better, even in such presumably susceptible patients. Flack et al. (1995) found linear associations of both systolic and diastolic BPs with the risk of coronary death in 5,362 patients with a history of myocardial infarction. Rodgers et al. (1996) also found a linear association of BP and stroke risk among 2,435 patients with a history of transient ischemic attacks or minor stroke. As noted by MacMahon et al. (1997):

> These two reports therefore provide reassurance that the observations of J- and U-shaped associations between BP levels and the risks of recurrent stroke and myocardial infarction are unlikely to indicate harmful effects of low BP. Moreover, they suggest the possibility that a sustained lower BP may be of benefit to many patients with preexisting cardiovascular disease. However, proof that BP lowering reduces the risks of recurrent myocardial infarction and stroke requires evidence from randomized trials.

Hypertension Optimal Treatment Trial

The Hypertension Optimal Treatment trial was designed to settle the controversy over whether the J-curve exists in patients with combined systolic and diastolic hypertension, by comparing outcomes among patients randomized to three different diastolic pressure goals (Hansson et al., 1998). In this prospective study, 19,000 patients with an average pretreatment pressure of 170/105 mm Hg were randomized to target diastolic pressure of not more than 90, 85, or 80 mm Hg. Treatment was begun with the long-acting dihydropyridine CCB felodipine, 5 mg once daily. Either an ACEI or a b-blocker and then a diuretic were added if the target diastolic BP

was not obtained with initial therapy.

A significant problem emerged that reduced the power of this study: Less separation in the diastolic BP was achieved among the three target groups than had been planned; the mean diastolic BPs obtained for the groups of not more than 90, 85, or 80 mm Hg were 85.2, 83.2, and 81.1 mm Hg, respectively. This close degree of BP reduction among the three groups failed to provide the power to detect any difference in protection with varying degrees of BP lowering. The data therefore did not disprove the existence of a J-curve.

In fact, the fewest major events and the lowest cardiovascular mortality were noted at average BPs of 138/83 and 139/85 mm Hg, respectively. Lower BPs did not further decrease or increase the number of adverse events, except for an apparent increase in mortality in those whose diastolic pressures were reduced to less than 70 mm Hg (Kaplan, 1998).

Evidence of a J-Curve with Isolated Systolic Hypertension

Among patients with ISH, two reports have suggested a J-curve for stroke when already low-normal diastolic levels are inadvertently lowered further by antihypertensive therapy (Somes et al., 1999; Vokó et al., 1999). First, as seen in Figure 5-8, in an average 4.7-year follow-up of 2,351 hypertensive patients older than 55 years (average age, 71.5 years), those who received antihypertensive therapy experienced a progressive decrease in the incidence of stroke as their diastolic pressures were lowered to the 65– to 74–mm Hg range, but a significant increase in stroke when the diastolic BP was lowered to less than 65 mm Hg (Vokó et al., 1999).

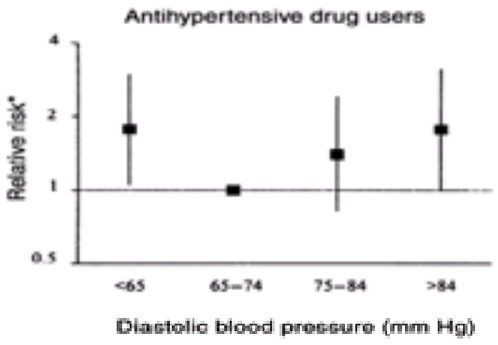


FIG. 5-8. Association between diastolic blood pressure and risk of first-ever stroke in 2,351 elderly hypertensives who were using antihypertensive drugs. Reference category is the second lowest category of diastolic blood pressure. Values are plotted on a logarithmic scale. *Adjusted for age, gender, smoking habit, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularization procedure), myocardial infarction, atrial fibrillation, and typical and atypical transient ischemic attack. (Reprinted from Vokó Z, Bots ML, Hofman A, et al. J-shaped relation between blood pressure and stroke in treated hypertensives. *Hypertension* 1999;34:1181–1185, with permission.)

Second, a reanalysis of the data from the SHEP trial involving 4,736 patients with initial average BPs of 177/77 mm Hg found a 14% increase in the risk for stroke among those whose diastolic pressures were inadvertently reduced by 5 mm Hg or more by active drug therapy (Somes et al., 1999). Those on treatment who did not have a cardiovascular event had an average diastolic BP of 68 mm Hg; those who did had an average diastolic BP of 65 mm Hg. It should be noted, however, that the risks were still less in those whose diastolic BPs were lowered than in those on placebo whose systolic levels remained elevated.

Recommendations for the Goal of Therapy

The optimal goal of antihypertensive therapy in most patients with combined systolic and diastolic hypertension who were not at high risk is a BP of less than 140/90 mm Hg. The greatest benefit is likely derived from lowering the diastolic pressure to 80 to 85 mm Hg. Not only is there no proved benefit with more intensive control, but also there is added cost and probable increased side effects associated with more aggressive antihypertensive therapy.

In elderly patients with ISH, the goal should be a systolic BP of 140 to 145 mm Hg, as that was the level reached in the RCTs wherein benefit was shown. Caution is advised if, inadvertently, diastolic pressures fall below 65 mm Hg. In such an event, less-than-ideal reductions in systolic levels need to be balanced against the potential of harm if diastolic levels fall below that level (Kaplan, 2001b).

In patients who start with a diastolic pressure between 90 and 94 mm Hg, lowering the BP by approximately 10 mm Hg appears to provide optimal cardiovascular protection (Cooper et al., 1988). More intensive therapy to attain a diastolic pressure of 80 mm Hg or lower may be desirable in some groups, including the following:

- Black patients, who are at greater risk for hypertensive complications and who may continue to have progressive renal damage despite a diastolic pressure of 85 to 90 mm Hg.
- Patients with diabetes mellitus, in whom a BP of less than 130/85 mm Hg reduces the incidence of cardiovascular events (Hansson et al., 1998). In the U.K. Prospective Diabetes Study population of 3,642 type 2 diabetic hypertensives, no threshold of risk for systolic pressure was noted: The lower the systolic BP down to 110 mm Hg, the lower was the risk of both micro- and macrovascular complications related to diabetes (Adler et al., 2000). (No data on diastolic pressures were provided.)
- Patients with slowly progressive chronic renal disease excreting more than 1 to 2 g of protein per day, in whom reducing the BP to 125/75 mm Hg may slow the rate of loss of renal function (Lazarus et al., 1997).

The Overriding Need: Adequate Therapy

Despite the concerns over a J-curve, we should not lose sight of the fact that the reason for the lesser protection found among most treated hypertensives reflects undertreatment, not over-treatment. Clearly, it is essential that all patients have their systolic BP brought down to 140 mm Hg and their diastolic BP to the 85– to 90–mm Hg range to provide the demonstrated benefits of therapy.

Importance of Population Strategies

Most of our current efforts are directed at the individual patient with existing hypertension. Clearly, we also need to advise the larger population to do those things that may protect against the development of hypertension, an approach directed toward “sick populations” rather than only sick individuals (Rose, 1992). Such population strategies likely should not involve medications but rather should be based on lifestyle modifications. The next chapter describes these modifications.

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6
Treatment of Hypertension: Lifestyle Modifications

With an appreciation of the benefits and costs of antihypertensive therapy, we now will consider the practical aspects of accomplishing a reduction in blood pressure (BP). In this chapter, *lifestyle modifications*—the term used rather than nondrug therapies—will be examined. At the end of this chapter, a number of miscellaneous therapies that are not lifestyle modifications are also covered. The next chapter covers the use of drugs.

THE PLACE FOR LIFESTYLE MODIFICATIONS

Lifestyle modifications are recommended to help treat hypertension in all current guidelines by expert committees (Campbell et al., 1999; Guidelines Subcommittee, 1999; Joint National Committee, 1997; Ramsay et al., 1999). When used together, these modifications provide very impressive reductions in BP (Sacks et al., 2001).

Perhaps even more important, lifestyle modifications may prevent hypertension (He et al., 2000). The evidence for their preventive potential remains fragmentary, and there is no proof that, individually or together, they will reduce hypertension-induced morbidity and mortality. However, the evidence that they will lower BP and reduce other major cardiovascular risk factors is incontrovertible (Ketola et al., 2000). Those who modify their lifestyle reduce the likelihood of heart attack, stroke, and diabetes (Wannamethee et al., 1998). Even though they are currently being underused (Silaste et al., 2000), appropriate lifestyle modifications, targeted for individual patients, will help to control hypertension (Weir et al., 2000) and reduce many of the accentuated cardiovascular risks that accompany aging (Kuller et al., 2001).

This book focuses on hypertension but, as noted throughout, the hypertensive patient is often endangered by the presence of concomitant risk factors. Most of the lifestyle changes described as helping to lower BP may also favorably affect these other risk factors. Cessation of smoking, weight loss, and regular physical activity certainly may improve coronary risk independent of their antihypertensive effects.

Potential for Prevention

An even greater possible value for lifestyle modifications is their potential for lowering the BP even a small amount in the overall population, delaying, if not preventing, the development of hypertension and thereby having a much greater impact than the high-risk approach of treating only those with established disease (Stamler, 1998). As summarized in Table 6-1, three long-term, well-controlled preventive trials involving subjects with high-normal BP have shown that individual and combined lifestyle modifications lower BP and reduce the incidence of overt hypertension (Hypertension Prevention Trial, 1990; Stamler et al., 1989; Trials of Hypertension Prevention, 1992, 1997).

Trial (reference)	No. of subjects	Duration (yr)	Weight loss (kg)	Reduction of incidence (%)
Primary prevention trial (Stamler et al., 1989)	201	5	2.7	54
Hypertension Prevention Trial (Hypertension Prevention Trial Research Group, 1990)	252	3	1.6	29
Trials of hypertension prevention				
I (Trials of Hypertension Prevention Collaborative Research Group, 1992)	564	1.5	3.9	51
II (Trials of Hypertension Prevention Collaborative Research Group, 1997)	565	4.0	1.9	21

TABLE 6-1. *Trials of lifestyle modifications on the incidence of hypertension*

The potential for lifestyle modifications to delay, if not stop, the development of hypertension is supported by data showing that the targets of lifestyle modifications are involved in the incidence and prevalence of hypertension. For example, in a prospective study of more than 40,000 U.S. women, the development of hypertension was directly associated with increasing caloric intake, body weight, alcohol consumption, and a diet poor in fruits and vegetables (Ascherio et al., 1996). In addition, the cross-sectional data from the 17,030 adults surveyed in the National Health and Nutrition Examination Survey III showed that systolic BP was positively associated with higher sodium, alcohol, and protein intakes and negatively associated with potassium intake (Hajjar et al., 2001).

A Structured Approach

As noted in Chapter 5, patients with hypertension can be categorized into levels of cardiovascular risk (Table 5-12 and Table 5-13). For those patients who fall into the lower risk categories, appropriate lifestyle changes should be the first and per-haps only therapy. As risk increases, so does the need for immediate antihypertensive drug ther apy. For those at higher risk with symptomatic cardiovascular disease (CVD), lifestyle changes should be instituted once the BP has come down to safer levels. There are obvious exceptions to this approach: If the patient is drinking more than three usual portions of alcohol-containing beverages per day, stopping or reducing that level may help to lower the BP even better than can drugs.

Even if lifestyle modifications are not them-selves totally effective in lowering the BP, they will mitigate many of the lipid and glucose-insulin abnormalities that often accompany hyper-tension and that may be aggravated by high doses of diuretics and b-blockers (Grimm et al., 1996). Therefore, all patients, regardless of risk status and the need for drugs, should also be enthusiastically encouraged to modify lifestyles at an appropriate time and in an appropriate manner.

The Issue of Efficacy

Some practitioners, although they recognize the potential benefits of lifestyle modifications, do not advise their patients to use them. There are two main reasons: First, it is too much trouble and, second, many patients do not implement the advice even if given. More time and effort undoubtedly are needed to instruct and motivate patients than to write out a prescription. However, various nonphysician practitioners—nurses, physician assistants, dietitians, psychologists—are available in most places, and they have been shown to be helpful in this effort (Miller et al., 1999). Although it is true that many patients do not modify lifestyle, poor cooperation is a major problem with drug treatment as well. The same techniques used to improve patient adherence to drug therapy, described in the next chapter, should help with both.

In a few trials, patients put on one or another lifestyle modification have been found to have diminished quality of life (Testa, 2000). However, no impairment of quality of life was noted by careful assessment after a longer than 3-year program of multiple lifestyle modifications in 508 hypertensive men (Agewall et al., 1995). Moreover, in the Treatment of Mild Hypertension Study, quality-of-life measures generally improved as the participants followed the lifestyle changes (Grimm et al., 1997; Neaton et al., 1993).

Nonspecific Effects

An antihypertensive effect has been claimed for virtually everything that has been tried, including some therapies that almost certainly are ineffective, such as dilute hydrochloric acid (Ayman, 1930) and cholecystectomy (Volini and Flax-man, 1939). Such claims are based on uncontrolled observation. As noted in Chapter 2, BPs tend to fall spontaneously for the first 6 to 12 weeks of observation, so that studies must be properly designed with adequate run-in periods or parallel observations of groups randomly allocated to lifestyle modifications or left untreated. Otherwise, what appear to be effects of the therapy may actually represent the usual fall in BP seen when repeated readings are taken. The same phenomenon likely is responsible for much of the initial response to drug therapy as well, so both drugs and nondrugs may be given credit deserved by neither.

Protection against Cardiovascular Disease

The larger issue of whether these lifestyle modifications will, in fact, reduce morbidity and mortality in hypertensive patients may never be settled. The difficulty of demonstrating such protection in the various therapeutic trials using much more potent antihypertensive drugs was described in Chapter 5. There is likely no way to document the efficacy of lifestyle modifications, which are less potent and more difficult to monitor than is drug treatment. Lifestyle modifications must be accepted on the evidence that they will lower the BP without risk and with a reasonable chance of adoption by most patients.

The situation was well described by Geoffrey Rose (1992):

> We can usefully distinguish two kinds of preventive measure. The first consists of removing or reducing some unnatural exposure in order to restore a state of biological normality (defined as the conditions to which we are thought to be genetically adapted through our evolutionary history). Examples would be stopping smoking, avoiding severe obesity, taking regular exercise, reducing the dietary intake of saturated fat and salt, and reducing chemical contamination of foods and of the environment. Such normalizing measures can be presumed to be generally safe, and they can therefore be accepted on the basis of a reasonable presumption of benefit.
>
> The second type of mass preventive measure is quite different, consisting not in removing a sup-posed cause of disease but in adding some other unnatural factor in the hope of conferring protection. This would include drugs (such as for the control of blood pressure or cholesterol), immunizations, and the use of unnatural doses of natural substances. For such measure there can be no prior presumption of safety, and hence the required evidence of benefit and (particularly) safety must be more stringent. This effectively rules out the use of these types of measure except where the offered benefit is rather large, i.e., in high-risk groups, or for common or serious hazards.

The dietary and other lifestyle changes recommended are neither unnatural nor potentially harmful, and they are increasingly needed to avert CVD. As shown in Chapter 3, our current high-fat, high-sodium, low-potassium, and low-calcium diet is unnatural; and it is getting worse, as more affluence and modernization threaten to turn the world into a Big Mac (Kant, 2000). We know what we should eat (Krause et al., 2000), but American children are increasingly eating what they should not eat, while sitting in front of a screen, avoiding physical activity, and becoming increasingly obese (O'Loughlin et al., 2000).

Before addressing the individual items of the overall lifestyle prescription shown in Table 6-2, evidence from studies that combined more than one of these items will be examined because, in clinical practice, they are usually used together. As will be noted, the effect of most of the individual lifestyle changes is to lower BP by as little as 1 to 2 mm Hg up to as much as 10 mm Hg. Patients who follow all these lifestyle modifications might then be expected to experience an impressive additive effect that could reduce BP by 15 to 20 mm Hg or more. That full additive effect is likely not seen for two reasons. First, some of the modifications likely lower BP through similar means; cessation of smoking, regular exercise, moderation of alcohol, and elimination of caffeine likely all work through reducing sympathetic nervous activity and so, when combined, they would likely not show full additive effects (Gordon et al., 1997). Second, even when patients are highly motivated, the degree of lifestyle change is often small, so the full effect of each is not seen.

Stop smoking
Lose weight if overweight
Reduce sodium intake to 110 mmol per day (2.4 g sodium or 6 g sodium chloride)
Maintain adequate dietary potassium, calcium, and magnesium intake
Increase physical activity
Limit alcohol intake to ≤1 oz per day of ethanol (24 oz of beer, 8 oz of wine, or 2 oz of 100-proof whiskey)

TABLE 6-2. *Lifestyle modifications for hypertension*

COMBINED THERAPIES

A number of studies of mild hypertension have shown that combinations of lifestyle modifications will lower BP while they reduce the amount of antihypertensive drugs needed to control the hypertension (Blumenthal et al., 2000; Sacks et al., 2001; Whelton et al., 1998). Two of these will be described in some detail: one because it applies to the largest group of hypertensives, the elderly, the other because it documents the pervasive benefit of dietary change in all populations.

The Trial of Nonpharmacologic Interventions in the Elderly (TONE) enrolled 975 men and women aged 60 to 80 years whose hypertension was controlled on one antihypertensive drug (Whelton et al., 1998). They were randomly assigned to reduced sodium intake, weight loss, both of these, or no intervention (i.e., usual care). After 3 months, their antihypertensive drug was withdrawn. Over the ensuing 30 months, the pro-portion of patients who remained normotensive without antihypertensive drugs was only 16% in those on usual care, more than 35% in those on one of the two interventions, and 43.6% in those on both interventions (Fig. 6-1). These impressive effects were achieved with relatively small amounts of dietary sodium reduction (an average of 40 mmol per day) or weight reduction (an average of 4.7 kg).

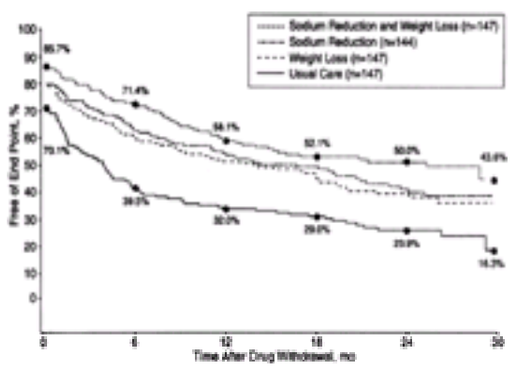

FIG. 6-1. Percentages of the 144 participants assigned to reduced sodium intake, the 147 assigned to weight loss, the 147 assigned to reduced sodium intake and weight loss combined, and the 147 assigned to usual care (no lifestyle intervention) who remained free of cardiovascular events and high blood pressure and in whom no antihypertensive agent was prescribed during follow-up. (Reprinted from Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the

treatment of hypertension in older persons. *JAMA* 1998;279:839–846, with permission.)

The second trial involved 412 adults whose average age was 48 years and who had a BP between 120 and 159 mm Hg systolic and 80 to 95 mm Hg diastolic (Sacks et al., 2001). They were randomly assigned to one of two diets, one typical of the U.S. diet (i.e., control), the other composed of more fruits, vegetables, and low-fat dairy foods [i.e., Dietary Approaches to Stop Hypertension (the DASH diet)]. In addition, they were randomly given one of three levels of sodium intake: high (150 mmol per day), intermediate (100 mmol per day), or low (50 mmol per day).

Each diet was consumed for 30 consecutive days, while weight was kept constant. Figure 6-2 graphically shows significant falls in systolic BP noted with the DASH diet at every level of sodium intake as compared to the control diet and significant falls in systolic BP with progressively lower sodium intakes on either diet. The effects were seen in normotensives and hypertensives, men and women, blacks and nonblacks, and were accompanied by falls in diastolic BP as well.

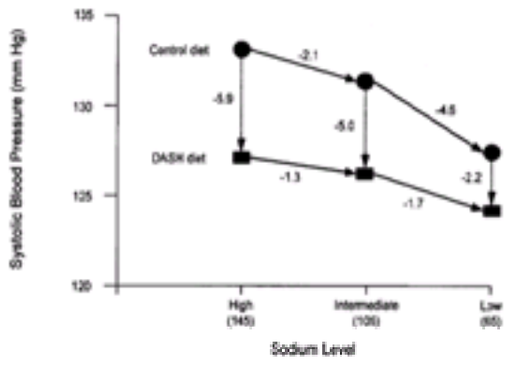

FIG. 6-2. Reduction of systolic blood pressure by dietary approaches to stop hypertension [the Dietary Approaches to Stop Hypertension (DASH) diet] and reduced sodium intake. The mean systolic blood pressures are shown for the high-sodium control diet. The three dietary sodium levels are expressed in terms of millimoles per day. The solid lines indicate changes in blood pressure for various sodium levels, and the dotted arrows show the mean differences in blood pressure between the two diets at each level of sodium intake.The order in which participants were given the sodium levels was random, with a cross-over design. There was a significant difference in systolic blood pressure between the high-sodium and low-sodium phases of the control diet (mean, –6.7 mm Hg) and the DASH diet (mean, –3.0 mm Hg). [Modified from Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med* 2001;344:3–10.]

Despite these impressive effects on BP, we have no definitive evidence of the overall effects of lifestyle modifications on morbidity or mortality, the type of information that is clearly needed to prove their value. Even though the economic costs of nutrition and exercise regimens may be as much as or greater than those of drug therapy (Johannesson and Fagerberg, 1992), these modalities improve both BP and cardiovascular risk status enough to support their use in the initial management of most hypertensives.

The effects of individual lifestyle modifications on hypertension will now be examined.

AVOIDANCE OF TOBACCO

Smoking cessation is the most effective, immediate way to reduce cardiovascular risk. This reduction in risk has long been thought not to involve an effect on BP because chronic smokers as a group have a lower BP than do nonsmokers (Mikkelson et al., 1997), likely because smokers weigh less than do nonsmokers. That is incorrect. The error arose because of the almost universal practice of having smokers abstain from smoking for some time before measuring their BP, usually because medical facilities are smoke-free. Thus, the significant, immediate, and repetitive pressor effect of smoking has been missed, because it lasts for only 15 to 30 minutes after each cigarette (see Fig. 3-38). Only with ambulatory BP monitoring has the major pressor effect of smoking been recognized (Mann et al., 1991; Oncken et al., 2001). The use of smokeless tobacco and cigars, if their smoke is inhaled, also may raise BP (Bolinder and de Faire, 1998).

This pressor effect must be at least partly responsible for the major increase in strokes and coronary disease among smokers (Wilson et al., 2000) as well as for their apparent resistance to antihypertensive therapy (Kawachi et al., 1994). The following are noxious cardiovascular effects of smoking:

- A worsening of lipid status (Craig et al., 1989)
- An increase in central obesity (Daniel et al., 1992)
- A worsening of insulin resistance (Rönnemaa et al., 1996)
- An attenuation of endothelium-dependent arteriolar dilatation (Celermajer et al., 1996)
- An increase in left ventricular mass (Amerena et al., 1997)
- Increased sympathetic nerve traffic (Narkiewicz et al., 1998)
- Increased arterial wall stiffness (Liang et al., 2001)
- A more rapid progression of renal insufficiency both in hypertensives (Regalado et al., 2000) and in patients with glomerular nephropathy (Stengel et al., 2000)

Thus, hypertensives who use tobacco must be repeatedly and unambiguously told to quit and given assistance in doing so (Lancaster et al., 2000). Nicotine patches may be effective and usually do not raise the BP (Tanus-Santos et al., 2001). Vigorous physical activity will help to prevent the usual gain in weight that occurs with smoking cessation (Marcus et al., 1999). If the patient continues to smoke, any antihypertensive drugs except nonselective b-blockers may attenuate the smoking-induced rise in BP (Pardell et al., 1998).

WEIGHT REDUCTION

The nature of modern life, with more caloric intake and less physical activity, engenders more obesity. Any degree of weight gain, even to a level that is not defined as overweight, is associated with an increasing incidence of hypertension and, even more strikingly, of type 2 diabetes (Willett et al., 1999). Even among those women whose body mass index (BMI) remained below the level defined as overweight (i.e., BMI >27), the incidence of hypertension increased threefold and the incidence of diabetes more than sixfold at a BMI of 26 as compared to a BMI of 21.

Because the maintenance of significant weight loss is so difficult for most who are obese (Craw-ford et al., 2000), physicians, patients, and society at large must do more to prevent weight gain. Simple measures, such as turning off children's television sets so that they become more physically active, will help (Robinson, 1999).

Clinical Data

Weight loss reduces BP in most overweight hypertensives (Stevens et al., 2001) and reduces the amount of antihypertensive drugs needed to control hypertension (Jones et al., 1999; Masuo et al., 2001a). The persistent antihypertensive effect of long-term weight loss was nicely documented in the Trials of Hypertension Prevention II study (Stevens et al., 2001). The study assigned 595 moderately obese subjects (10% to 65% above ideal body weight) with high-normal BP (diastolic BPs, 83 to 89 mm Hg) to an intensive weight loss program and compared them to another 596 subjects who were left alone. Over the 3-year follow-up, only 13% of the active participants were able to maintain a substantial weight loss of 4.5 kg or more but, as shown in Figure 6-3, those subjects experienced a significant fall in BP and a 65% lower relative risk for the onset of hypertension as compared to the control group. Even those for whom weight loss was not sustained (i.e., the relapse group) had a 25% lower risk for developing hypertension by the end of the 3 years.

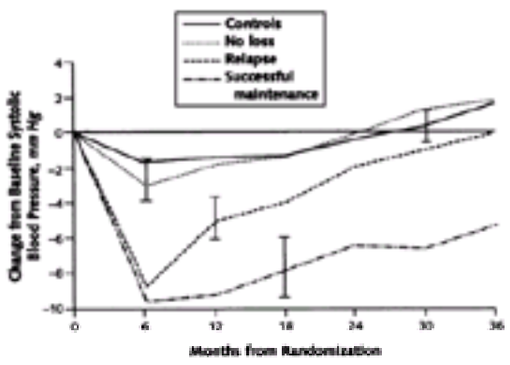

FIG. 6-3. Long-term changes in weight and systolic blood pressure. Data are adjusted for age, ethnicity, and gender, according to patterns of weight change. Usual-care controls were not assigned to intervention. Participants with successful maintenance of weight loss were defined as those who lost 4.5 kg or more at 6 months and maintained at least 4.5 kg of weight loss at 36 months. Participants with relapse were those who lost at least 4.5 kg at 6 months but whose weight loss at 36 months was less than 2.5 kg. Participants registered as having no weight loss had weight loss of 2.5 kg or less at 6 and 36 months. Error bars represent 95% confidence intervals. (Modified from Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med* 2001;134:1–11.)

Mechanisms of Antihypertensive Effect

Weight loss likely lowers BP through multiple effects, including the following:

- An improvement in insulin sensitivity (Dengel et al., 1998), which may result in a decrease in visceral fat (Marks et al., 1998)
- A decrease in sympathetic nervous system activity (Masuo et al., 2001b), probably due to an improvement in baroreflex control (Grassi et al., 1998)
- Decreases in plasma leptin levels (Ogawa et al., 2000)
- Reversal of endothelial dysfunction revealed by increased nitric oxide–induced vasodilation (Perticone et al., 2001)

Recommendations for Implementation

A structured, lower-calorie diet, along the lines of the Weight Watchers program, should be advised while avoiding “crash” diets and the latest fad of the moment. The ability to lose weight is greatly enhanced by an accompanying regularly performed program of physical activity (Jakicic et al., 1999). It takes a fairly vigorous exercise to overcome the decline in resting metabolic rate that occurs during dieting (Geliebter et al., 1997). An average of 80 minutes per day of moderate activity or 35 minutes per day of vigorous activity are needed to prevent weight gain after successful weight loss (Schoeller et al., 1997).

A variety of pharmacologic aids are available and, as in the treatment of hypertension or diabetes, will increasingly be used for as long as obesity persists (McMahon et al., 2000; Sjöström et al., 1998). Those agents that sup-press appetite, such as sibutramine, should be used only in concert with diet and exercise because, by themselves, they may raise BP (James et al., 2000). More such therapies are being developed (Bouchard, 2000; Mertens and Van Gaal, 2000). Meanwhile, prepared meal plans may be useful (Metz et al., 2000).

SODIUM REDUCTION

Although dietary sodium reduction had been shown to lower BP by Ambard in 1906 and Allen in 1920, it was Kempner (1948) who popularized rigid sodium restriction at a time when little else was available for therapy of hypertension. Kempner's rice diet was shown to be effective because it was so low in sodium (Watkin et al., 1950).

After thiazides were introduced during the late 1950s and their mode of action was shown to involve a mild state of sodium depletion, both physicians and patients eagerly adopted this form of therapy in place of dietary sodium reduction. In discarding rigid salt restriction, physicians disregarded the benefits of modest reduction both for its inherent antihypertensive effect and for its potential of reducing diuretic-induced hypokalemia. Moreover, the amount of sodium chloride ingested by some patients—15 to 20 g per day– may completely overcome the antihypertensive effectiveness of diuretics (Winer, 1961).

To avoid confusing the terms *salt* and *sodium* (which is 40% of sodium chloride), only *sodium* will be used in this text, as it is on food labels. As noted in Chapter 3, the chloride anion is important for the expression of sodium's effects, and most sodium is ingested in the form of table salt or sodium chloride. In other forms, such as sodium bicarbonate, sodium poses little or no pressor effect (Schorr et al., 1996).

General Recommendations

Moderate sodium reduction to a level of 2.4 g per day (6 g NaCl per day, 110 mmol per day) for both prevention and treatment of hypertension has been included in all of the recent guidelines from expert committees (Guidelines Subcommittee, 1999; Joint National Committee, 1997; Ram-say et al., 1999), governmental reports (Dietary Guidelines Advisory Committee, 1995), and voluntary health agencies (Krause et al., 2000). As will be described in the next few pages, the evidence for the benefits of such reduction extend beyond the lowering of BP and, thereby, a reduction in cardiovascular morbidity and mortality. At the same time, such moderate reduction has been shown to be generally well accepted, relatively easily obtained, and free from adverse effects.

A Dissenting View

However, there are dissenters to the value of such moderate sodium reduction. Their dissent is based on two major points: first, that moderate sodium reduction will not lower BP; second, that such reduction will likely cause hazards that would outweigh its benefits (Alderman, 2000; Swales, 2000). In addition to the concerns expressed by these dissenters, the possible loss of income to the salt and soft-drink industries that might follow moderate sodium reduction has led to the formation of lobbying operations in several countries that work against efforts to reduce sodium consumption.

Putative Dangers

The first point of the dissenters, that moderate sodium reduction will not lower BP, is clearly wrong, as will be documented in the next section. The second point, that such reduction will have hazards that outweigh any possible benefits, is harder to disprove with absolute certainty in the absence of large controlled trials, which likely will not and cannot be performed. However, the putative dangers have largely been shown not to exist (Kumanyika and Cutler, 1997). These putative dangers include the following:

- *An increase in myocardial infarction* (Alder-man et al., 1995). These data, based on a single urine collection after 5 days on a diet including lower sodium intake, showed an increase in myocardial infarctions (but not strokes) in men (but not women) who were followed up for 3.8 years. These data have been faulted because of the small number of events (46 in 2,937 subjects), the failure to ascertain long-term sodium intake, and the likely presence of multiple con-founding factors (Cook et al., 1995).
- *An increase in mortality* (Alderman et al., 1998). These data, based on a single-day dietary recall, showed an increased all-cause mortality the lower the sodium intake in a representative sample of 20,729 U.S. adults, approximately half of whom were traced 20 years later. These data have been attacked even more vociferously, mainly for the weakness of the measure of sodium intake, resulting in a level so low (30 mmol per day) as to be impossible to achieve in a free-living population; the presence of known and (likely) unknown confounding factors; and the inability to ascertain long-time sodium intake (de Wardener, 1999; Poulter, 1998).

Of interest, as shown in Figure 6-4, when these same data were looked at separately for the 6,797 nonobese and the 2,688 obese sub jects, highly significant direct associations between increased sodium intake and stroke, coronary heart disease, and cardiovascular and all-cause mortality were found among the obese subjects (He et al., 1999). Because obesity com monly accompanies hypertension, these data are at the least reassuring that sodium reduction is not hazardous, although they suffer from some of the same methodological problems associ ated with the data of Alderman et al. (1998).

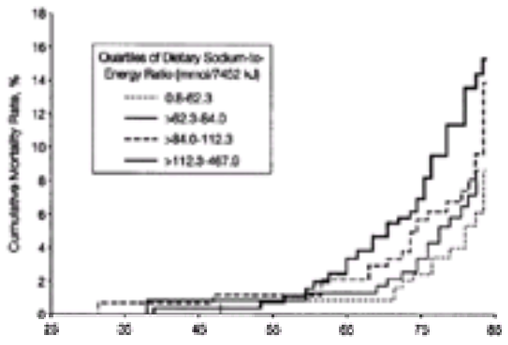

FIG. 6-4. Cumulative mortality from stroke over an average follow-up of 19 years according to baseline dietary sodium-to-energy ratio in 2,688 obese subjects included in the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. (Modified from He J, Ogden LG, Vupputuri S, et al. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA* 1999;282:2027–2034.)

Methodologically stronger prospective data from Finland further document the positive correlation between higher sodium intake, ascertained from 24-hour urinary sodium excretion, and the risk of coronary heart disease in men, an association that was independent of other risk factors including BP and also primarily seen in those who were over-weight (Tuomilehto et al., 2001).

- *Potentially harmful perturbations in various hormonal, lipid, and physiologic responses* (Graudal et al., 1998). These perturbations occur only when sodium intake has been severely restricted down to 10 to 20 mmol per day and usually for only 4 to 10 days.

Severe versus Moderate

A few examples will show the need to keep such artificial, brief, severe sodium restriction separate from the recommended, attainable moderate reduction, something that some authors fail to do when they impugn the safety of sodium reduction (Graudal and Galløe, 2000).

- Brief, severe sodium restriction increases plasma catecholamines (Gomi et al., 1998); prolonged, moderate sodium reduction lowers plasma catecholamines (Beckman et al., 1995).
- Brief, severe sodium restriction increases serum low-density lipoprotein cholesterol and triglycerides (Egan and Stepniakowski, 1997); moderate reduction does not (Fotherby and Potter, 1997).
- Brief, severe sodium restriction increases insulin resistance (Gomi et al., 1998); moderate reduction does not (Grey et al., 1996).
- Brief, severe sodium restriction may reduce the intake of other useful nutrients (Morris, 1997); moderate reduction does not (Korhonen et al., 2000).
- Rats on a very-low-sodium diet are unable to respond to volume losses from heat exposure (Ely 1997); in humans, moderate sodium reduction causes no impairment in the ability to exercise vigorously even in hot environments (Hargreaves et al., 1989).

Having considered the putative dangers of sodium reduction, we will now turn to the other issue raised by dissenters: the lack of an effect on BP.

Clinical Data

Beyond the more recent documentation of the ability of moderate sodium reduction to lower BP in the TONE (Whelton et al., 1998) and DASH-sodium (Sacks et al., 2001) trials (Fig. 6-1, Fig. 6-2), a large body of controlled trial data shows that, in hypertensives, when sodium intake is reduced to approximately 100 mmol per day, the BP falls an average of 4.8 ± 1.0 mm Hg systolic and 2.45 ± 0.7 mm Hg diastolic (Cutler et al., 1997) (Fig. 6-5). Even greater average effects of moderate sodium reduction were noted by Law et al. (1991) in their analysis of 68 crossover trials and 10 randomized, con-trolled trials of sodium reduction. Although their analysis has been criticized for its inclusion of poorly controlled data (Swales, 2000), Law et al. (1991) documented that the effectiveness of sodium reduction increases with increasing initial BP levels and increasing age; they also documented the need for patients to remain on the reduced diet for at least 5 weeks to observe the full effect.

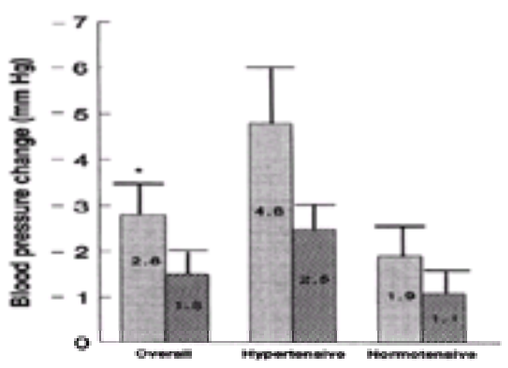

FIG. 6-5. Mean net changes in systolic (*stippled bars*) and diastolic (*striped bars*) blood pressure, with 95% confidence intervals, pooled for all sodium-reduction trials and for various subsets. *Mean change as compared with control, with upper 95% confidence interval. [Modified from Cutler JA, Follman D, Allender PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr* 1997; 65(Suppl):643S–651S.]

Elderly hypertensive subjects respond particularly well (Cappuccio et al., 1997), perhaps because their hypertension is more volume-dependent, in keeping with their lower plasma renin levels (Niarchos et al., 1984). This fact has been confirmed by a metaanalysis by Midgley et al. (1996) of 28 randomized, controlled trials that included 1,131 hypertensive subjects who had an average urinary sodium reduction of 95 mmol per day. They noted an average decrease in BP of 3.7/0.9 mm Hg in all 28 trials but a 6.3/ 2.2–mm Hg decrease in the 17 trials involving patients aged 45 or older.

In addition to lowering BP, other benefits have been observed with moderate sodium reduction, as summarized in Table 6-3.

Enhancement of efficacy of antihypertensive drugs (Chrysant et al., 2000)
Reduction of diuretic-induced potassium loss (Crippa et al., 1996)
Regression of left ventricular hypertrophy (Messerli et al., 1997)
Reduction in proteinuria (Weir et al., 1995)
Reduction in urine calcium excretion (Sakhaee et al., 1993)
Decrease in osteoporosis (Martini et al., 2000)
Decreased prevalence of stomach cancer (Joossens et al., 1996)
Decreased prevalence of stroke (Sasaki et al., 1995)
Decreased prevalence of asthma (Peat, 1996)
Decreased prevalence of cataract (Cumming et al., 2000)
Protection against onset of hypertension (Geleijnse et al., 1996; He et al., 2000)

TABLE 6-3. *Additional benefits of moderate sodium reduction*

Enhancement of Efficacy of Antihypertensive Drugs

Moderate sodium reduction clearly increases the antihypertensive efficacy of all classes of antihypertensive drugs, with the possible exception of calcium channel blockers (Chrysant et al., 2000; Morgan et al., 1986). As is noted in Chapter 7, calcium channel blockers have an intrinsic natriuretic effect, which may explain the lesser potentiation with sodium reduction. Nonetheless, moderate sodium reduction will enhance the antiproteinuric effect of nondihydropyridine calcium channel blockers as well as of angiotensin-converting enzyme inhibitors (Bakris and Weir, 1996).

Protection from Diuretic-Induced Potassium Loss

High levels of dietary sodium make patients more vulnerable to the major side effect of diuretic therapy, hypokalemia. The diuretic inhibits sodium reabsorption proximal to that part of the distal convoluted tubule where secretion of potassium is coupled with sodium reabsorption under the influence of aldosterone. When a diuretic is given daily while the patient ingests large amounts of sodium, the initial diuretic-induced sodium depletion shrinks plasma volume, activating renin release and secondarily increasing aldosterone secretion. As the diuretic continues to inhibit sodium reabsorption, more sodium is delivered to this distal site. The increased amounts of aldosterone act to increase sodium reabsorption, thereby increasing potassium secretion, and the potassium is swept into the urine.

With modest sodium reduction (70 to 100 mmol per day), less sodium is delivered to the distal exchange site, and therefore less potassium is swept into the urine. This modest restriction should not further activate the renin-angiotensinaldosterone mechanism to cause more distal sodium-for-potassium exchange, because that usually occurs only with more rigid sodium restriction. This postulate was confirmed in a test of 12 hypertensive patients who were given one of three diuretics for 4-week intervals while ingesting a diet inclusive of either 72 or 195 mmol per day of sodium (Ram et al., 1981). While on the modestly restricted diet, total body potassium levels fell only half as much. Similar results have been observed with the diuretic indapamide (Crippa et al., 1996).

Sodium Sensitivity and Cardiovascular Risk

As detailed in Chapter 3, varying degrees of BP sensitivity to varying levels of sodium intake have been documented in both normotensive and hypertensive people. By definition, those who are more sodium-sensitive have a greater fall in BP with dietary sodium reduction (Chrysant et al., 1997). Those who are more sodium-sensitive tend to have less of a nocturnal fall in BP (i.e., nondipping) (Suzuki et al., 2000), which may be involved in their amply documented increased risk for cardiovascular (Morimoto et al., 1997) and renal (Bihorac et al., 2000) target organ damage and mortality (Weinberger et al., 2001) as compared to sodium-resistant patients. These findings strengthen the need for sodium reduction to reduce the increased risks that accompany sodium sensitivity.

There seems to be no need to ascertain the individual patient's degree of sodium sensitivity before recommending moderate sodium reduction, particularly as testing may not be reliable or reproducible (Gerdts et al., 1999). Those who respond more to sodium reduction likely are more sodium-sensitive, but there is no harm and, as noted in Table 6-3, there are other potential benefits of moderate sodium reduction in all hypertensives. In view of the proved increased risk of cardiovascular and renal damage from higher sodium intake in hypertensives (du Cailar et al., 2000), all should be encouraged to reduce their levels to the 100- to 110-mmol per day goal.

Additional Benefits

Of the additional benefits of moderate sodium reduction shown in Table 6-3, perhaps the most certain is the reduction in urinary calcium excretion, protecting against renal stones and osteoporosis, whereas the most exciting is the potential for prevention of hypertension, as suggested by the lower BP at age 15 of children who had been on a lower sodium intake as babies (Geleijnse et al., 1997).

Mechanisms of Antihypertensive Effect

Despite considerable research, the mechanisms by which moderate sodium restriction lowers BP are not well characterized. After 6 months on a 120-mmol per day sodium diet, during which casual BP was reduced by 8/5 mm Hg, cardiac output was slightly reduced but peripheral resistance was not changed (Omvik and Myking, 1995). Others have noted improved arterial distensibility (Avolio et al., 1986), decreased plasma atrial natriuretic hormone levels (Jula et al., 1992), and improved b-adrenergic responsiveness (Feldman, 1992), but how these affect BP is uncertain. On the other hand, the structure and function of the heart and kidneys may be improved after pro-longed, moderate sodium reduction: Left ventricular hypertrophy decreases (Messerli et al., 1997), and glomerular hyperfiltration and proteinuria are reduced (Weir et al., 1995).

The fall in BP tends to be greater in those with low plasma renin levels that rise little during sodium restriction (He et al., 1998). Such patients may be among the nonmodulators described by Williams and Hollenberg (1991) (see Chapter 3). As noted in Chapter 3, the BP sensitivity to sodium tends to be enhanced in hypertensives, particularly if they are black and older, so that these patients tend to respond more to sodium reduction (Weinberger, 1996).

Recommendations for Implementation

With the caveat that rigid sodium restriction may be counterproductive by turning on the reninaldosterone mechanism, it should be noted that even when strong and repeated attempts are made to reduce dietary sodium intake, the usual level reached is approximately that which was recommended, a 25% to 30% reduction, from the usual average of 150 to 175 mmol per day down to 100 to 120 mmol per day (Kumanyika et al., 1993). When special efforts are made, such as providing all the food in the DASH trial (Sacks et al., 2001) or with intensive, positive-feedback behavioral modification (Luft et al., 1997), even more impressive sodium reduction can be achieved.

Fortunately, the 40- to 60-mmol per day reduction that is needed should be relatively easily reached by avoiding highly salted processed foods (Beard, 1997). In the United States that reduction has been made much easier by the requirement that all packaged foods have their sodium content on the label. Because processed foods are the source of more than 75% of sodium intake in the U.S. diet, only a few natural, low-sodium (and high-potassium) foods need be substituted for processed, high-sodium (and low-potassium) foods. For example, 6 oz of canned tomato juice has 660 mg of sodium; 6 oz of fresh orange juice has 2 mg. Replacement of table salt with a salt substitute may also be helpful (Geleijnse et al., 1994).

The goal of a lower sodium intake would be greatly facilitated if food processors gradually reduced the amount of sodium added to their products (Engstrom et al., 1997). Because the preference for sodium is quickly reduced when less sodium is ingested (Mattes, 1997), people can be satisfied by foods with less sodium (Adams et al., 1995; Rodgers and Neal, 1999).

In addition to the “salt mines” of certain processed foods, some antacids such as Alka-Seltzer, injectable antibiotics, and bottled waters may have large amounts of sodium (Yarows et al., 1997). Beyond difficulties in avoiding highly salted foods, the elderly may lose some of their perception of the saltiness of foods and therefore

add even more to satisfy their taste (Schiffman, 1997).

Conclusions

High sodium intake is harmful (Tuomilehto et al., 2001), and moderate sodium reduction is worth-while and feasible. The reduction of BP possible with a universal reduction in sodium intake of 50 mmol per day down to the recommended level of 100 to 110 mmol per day has been estimated to translate into a 22% reduction of the incidence of stroke and a 16% reduction in the incidence of coronary disease (Law, 1997). Such estimates may be valid: Repeated surveys from 1966 to 1986 in Belgium showed a progressive decrease in average sodium intake from 203 to 144 mmol per day; these falls correlated closely with lesser rises in BP with increasing age and decreased stroke mortality in the population (Joosens and Kesteloot, 1991). Such population-wide reductions in sodium intake are likely both to improve health and reduce costs to society (Selmer et al., 2000). As confirmed in a recent workshop that reviewed all the evidence of sodium and BP (Chobanian and Hill, 2000), the real potential for benefit, with the remote possibility of harm, makes moderate sodium reduction a desirable goal both for the individual hypertensive patient and for the population at large.

POTASSIUM SUPPLEMENTATION

Many of the benefits of reduced sodium intake could reflect an increased potassium intake, although in the TONE study the antihypertensive effects of the two were independent of each other (Espeland et al., 2001). Epidemiologic evidence supports an inverse relationship between potassium intake and BP (He and Whelton, 1999), particularly among blacks (Morris et al., 1999). Short-term potassium depletion exacerbates hypertension (Krishna and Kapoor, 1991) and, in blacks, enhances pressor responses to stress (Sudhir et al., 1997).

Clinical Data

He and Whelton (1999) identified 33 randomized, controlled trials of the effect of oral potassium supplementation on BP, 20 in hypertensives. A pooled analysis of the 33 trials found an overall reduction of 4.4/2.5 mm Hg (Fig. 6-6). Greater effects were seen in the 28 trials wherein potassium excretion was increased by 20 mmol per day or more and in the 28 trials wherein no antihypertensive drugs were given. Overall, the response was greater in blacks, the higher the baseline BP and the greater the sodium intake.

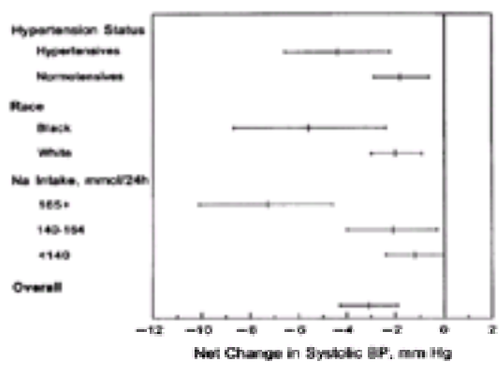

FIG. 6-6. Pooled net change in systolic blood pressure (BP) by participants' characteristics in 33 randomized, controlled trials of potassium supplementation. Na, sodium. (Reprinted from Jiang H, Whelton PK. What is the role of dietary sodium and potassium in hypertension and target organ injury? *Am J Med Sci* 1999;317: 152–159, with permission.)

In 300 normotensive, middle-aged women in the Nurses Health Study whose reported potassium intake was low, potassium supplements of 40 mmol per day over 16 weeks provided a 2.0/ 1.7–mm Hg fall in mean 24-hour ambulatory BP (Sacks et al., 1998).

The potassium supplement in almost all these trials was potassium chloride (KCl), given in amounts from 48 to 120 mmol per day. Two randomized, controlled trials have found a greater fall in BP after either potassium citrate (Over-lack et al., 1995) or potassium bicarbonate (Morris et al., 1995) than after equal amounts of KCl, which was essentially ineffective in both trials.

Protection against Strokes

Increased potassium intake may protect against strokes. This was suggested by Acheson and Williams (1983) and was supported by the finding that an increase in potassium intake of 10 mmol per day was associated with a 40% reduction in stroke mortality among 859 older people (Khaw and Barrett-Connor, 1987). Among men in the Framingham Heart Study, an increased intake of three servings per day of potassium-rich fruits and vegetables was associated with a 22% lesser risk for stroke over a 20-year follow-up (Gillman et al., 1995). In three even larger populations, increased dietary potassium intake was associated with fewer strokes (Ascherio et al., 1998; Fang et al., 2000) and lower all-cause mortality (Tunstall-Pedoe, 1999). These findings are supported by studies that demonstrate protection by high-potassium diets against vascular damage in the brain and kidneys of susceptible rats (Tobian, 1997) and various animal models (Young and Ma, 1999).

Mechanisms of Antihypertensive Effect

At least seven possible mechanisms have been proposed by which potassium may lower BP and protect against CVDs (Young and Ma, 1999):

- Inhibition of free radical formation and low-density lipoprotein oxidation
- Inhibition of proliferation of vascular smooth muscle cells
- Inhibition of platelet aggregation and arterial thrombosis
- Reduction in renal vascular resistance and increase in glomerular filtration rate
- Vascular relaxation by enhanced vascular Na^+/ K^+–adenosine triphosphatase activity (Dolson et al., 1995)
- A natriuresis (Singh and Linas, 1993)
- A reduction in pressor sensitivity to sodium (Morris et al., 1999), which, in turn, may convert nocturnal BP from a nondipping to a dip-ping status (Wilson et al., 1999)

Recommendations for Implementation

Even though potassium supplements may lower the BP, they are too costly and potentially hazardous for routine use in the treatment of hyper-tension in normokalemic patients. They are indicated for diuretic-induced hypokalemia and, in the form of potassium-containing salt substitutes, will add little expense. For the larger population, a reduction of high-sodium–lowpotassium processed foods with an increase of low-sodium–high-potassium natural foods is all that likely is needed to achieve the potential benefits. Fruits and beans provide the largest quantity of potassium per serving.

CALCIUM SUPPLEMENTATION

A large number of often conflicting epidemiologic studies and therapeutic trials have examined the connection between calcium intake and BP. There appears to be an inverse relation between dietary calcium intake and BP so that increased dairy consumption could help prevent hypertension as well as osteoporosis (Power et al., 1999). However, both dietary and nondietary calcium supplements have a minimal effect on BP, an effect too small to recommend their use to treat hypertension.

As noted in Chapter 11, calcium supplements during pregnancy have been found to protect against preeclampsia in some groups but not in otherwise healthy U.S.

women.

Clinical Data

Griffith et al. (1999) performed a metaanalysis of all 42 randomized, controlled trials available as of May 1997 of either dietary (dairy) or non-dietary supplements of calcium. The pooled analysis found a reduction in BP of –1.44/0.84 mm Hg, with a trend toward larger effects with dietary supplements but with statistically significant heterogeneity of results across trials (Table 6-4). However, as Cappuccio (1999) noted, the dietary trials almost all included other ingredients that could have contributed to an antihypertensive effect. For example, in the DASH trial, calcium intake was increased by 800 mg but fiber was increased by 240%, potassium by 150%, magnesium by 173%, and protein by 30%. Therefore, the possibility of a greater effect from dietary sources of calcium must be taken with a grain of salt.

Blood pressure type	Mean change (mm Hg) in blood pressure (95% confidence interval)
All studies (n = 42)	
Systolic blood pressure	−1.44 (−2.20, −0.68)
Diastolic blood pressure	−0.84 (−1.44, −0.24)
Dietary (n = 9) and nondietary (n = 33) interventions	
Systolic blood pressure	
Dietary	−2.10 (−2.93, −1.26)
Nondietary	−1.09 (−2.12, −0.06)
Diastolic blood pressure	
Dietary	−1.09 (−1.67, −0.52)
Nondietary	−0.87 (−1.71, −0.03)

Reprinted from Griffith LE, Guyatt GH, Cook RJ, et al. The influence of dietary and nondietary calcium supplementation on blood pressure. *Am J Hypertens* 1999;12:84–92, with permission.

TABLE 6-4. *Summary estimates using random effects model of systolic and diastolic blood pressure in 42 randomized, controlled trials comparing calcium supplementation with placebo*

Studies published since mid-1997 support a very limited effect of 1 to 2 g per day of calcium supplements on BP (Bostick et al., 2000; Kawano et al., 1998b). Similarly, no effect on BP was seen with 1200 mg of calcium given to women whose habitual intake was low (Sacks et al., 1998).

Mechanisms of Antihypertensive Effect

If some patients do respond to calcium supplementation, they likely are those who have a mild degree of secondary hyperparathyroidism that arises to compensate for increased urinary calcium excretion that, in turn, reduces plasma ionized calcium levels. The entire sequence may very well begin with high sodium intake, which causes volume expansion in sodium-sensitive, low-renin patients and leads to increased urinary calcium excretion (Kaplan, 1988) (Fig. 6-7). Support for this concept comes from the finding that those who respond to supplemental calcium tend to be those with low serum calcium and high parathyroid hormone levels (Lyle et al., 1988; Resnick, 1989). Moreover, in 16 healthy individuals given 2 g per day of calcium for 16 weeks, Petrov and Lijnen (1999) found an increase in urinary calcium excretion and a decrease in plasma parathyroid hormone levels but no change in plasma calcium.

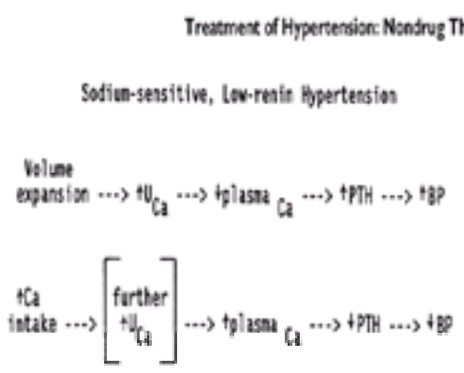

FIG. 6-7. A potential explanation for a hypotensive action of increased dietary calcium intake. BP, blood pressure; Ca, calcium; PTH, parathyroid hormone. (Modified from Kaplan NM. Calcium and potassium in the treatment of essential hypertension. *Semin Nephrol* 1988;8:176–184.)

Recommendations for Implementation

In the absence of data showing a significant effect of calcium supplementation on BP, this approach is not recommended for treatment of hypertension. As shown in Figure 6-7, calcium supplements may increase further the hypercalciuria already present in many hypertensives and thereby lead to kidney stones and urinary tract infection (Curhan et al., 1997; Peleg et al., 1992). Until there is a simple way to determine calcium sensitivity, the best course is to ensure an adequate dietary calcium intake but not to give calcium supplements to either prevent or treat hypertension.

MAGNESIUM SUPPLEMENTATION

The advice given for calcium supplements seems to be appropriate in regard to magnesium as well. The theoretic connection between magnesium deficiency and hypertension is more direct and logical than that between calcium and hypertension (Gilbert D'Angelo et al., 1992), but serum and intracellular magnesium levels are normal in most untreated hypertensives (Delva et al., 1996). However, low muscle magnesium concentration has been found in half of patients on chronic high-dose diuretic therapy (Drup et al., 1993), and magnesium deficiency usually is responsible when hypokalemia is not corrected by potassium repletion (Whang et al., 1992). Moreover, low dietary magnesium intake was associated with a higher incidence of hypertension in the U.S. female nurse study (Ascherio et al., 1996). How-ever, no significant effect on the BP of those nurses with low habitual intake of magnesium was seen with magnesium supplements (14 mmol per day for 16 weeks) (Sacks et al., 1998).

In hypertensive patients, magnesium supplements may provide a small but statistically significant fall in BP. In an 8-week crossover study, 60 hypertensives (average BP, 149/90 mm Hg) had an average 2.5/1.4–mm Hg fall in 24-hour ambulatory readings after 8 weeks of 20-mmol per day magnesium supplementation (Kawano et al., 1998a). Rather than giving magnesium supplements, increasing dietary consumption with fresh fruits and vegetables seems preferable. Part of the impressive effects of the DASH diet may reflect its 173% higher magnesium content (Cappuccio, 1999). Magnesium supplements should be given to patients found to be magnesium-deficient. For those patients, 15 mmol per day of magnesium may lower BP, enable potassium to be replenished, and improve glucose metabolism (Paolisso et al., 1992).

INCREASED PHYSICAL ACTIVITY

At the same time as the evidence for protection from CVD and all-cause mortality by regular physical activity has become incontrovertible (Church et al., 2001; Hu et al., 2001; Snell and Mitchell, 1999), most Americans (Caspersen et al., 2000), and likely people in all industrialized societies (van Mechelen et al., 2000), are becoming less physically active in their daily lives. Therefore, increased physical activity must be strongly encouraged for all people, perhaps even more so for hypertensives, as it may also lower their BP. In those who wish to engage in competitive athletics, hypertension in the absence of tar-get organ damage or concomitant heart disease should not limit eligibility (Maron et al., 2001).

Clinical Data

Regular aerobic exercise is almost always accompanied by a lowering of BP (Blumenthal et al., 2000; Hagberg et al., 2000). After each 30 period of aerobic exercise at 50% of maximal oxygen uptake, the BP remains lower for the rest of the 24-hour period, with an even greater reduction for the rest of the day after 30 minutes at 75% of maximal oxygen uptake (Quinn, 2000). The effect is seen in elderly hypertensives (Taylor-Tolbert et al., 2000) and may be even greater in those with certain genotypes involving endothelial nitric oxide synthesis (Rankinen et al., 2000) or angiotensinogen (Rauramaa et al., 2000). Those who exercise have less risk of stroke (Rodriguez et al., 2000) and slower progression of atherosclerosis (Lakka et al., 2001).

Normotensive people achieve a slight fall in BP with aerobic exercise (Wilmore et al., 2001), which may be enough to reduce significantly their risk for developing hypertension (Hayashi et al., 1999; Pereira et al., 1999) or diabetes (Folsom et al., 2000; Wei et al., 1999). Regular aerobic exercise blunts an exaggerated BP response during exercise stress testing, which is an independent risk factor for development of hypertension (Miyai et al., 2000).

Because the systolic BP rises during exercise and because the abrupt rise in BP after arising from sleep is associated with an increased incidence of cardiovascular events, concerns about exercise in the morning have been raised. How-ever, even in patients with known coronary disease, no increase in events was noted with exercise performed in the morning versus the afternoon (Murray et al., 1993). On the other hand, strenuous physical exertion in patients who are habitually sedentary may precipitate an acute myocardial infarction, whereas habitual vigorous exercise reduces the risk of sudden death during exercise (Albert et al., 2000), so patients should always be advised to increase their level of activity slowly.

Two additional facts about the benefits of physical activity have been recognized. First, progressive resistance exercise (i.e., moving against resistance as with Nautilus-type equipment) also lowers BP (Kelley and Kelley, 2000), unlike pure isometric exercise, which induces a marked immediate pressor response. Second, even though a greater fall in BP is seen with progressively more vigorous exercise (Fig. 6-8), the major benefits of exercise can be achieved with ordinary physical activity (Dunn et al., 1999), including walking (Hayashi et al., 1999). By integrating moderate-intensity physical activity into their daily lives, people can obtain all the cardiorespiratory benefits of a structural exercise program at a far lower cost (Sevick et al., 2000).

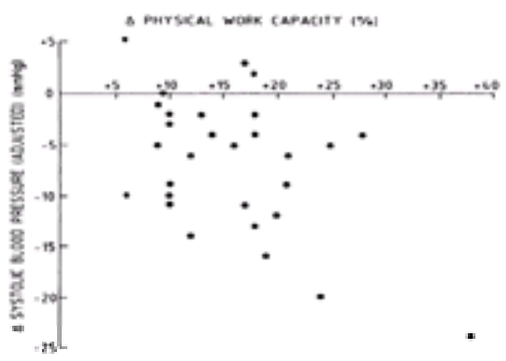

FIG. 6-8. Change in systolic blood pressure with training, adjusted for control data, versus change in physical work capacity. Each point represents the average for one group of subjects (n = 29; r = –0.49; p <–.01). (Reprinted from Fagard R, Bielen E, Hespel P, et al. Physical exercise in hypertension. In: B Brenner, J Laragh, eds. *Hypertension: pathophysiology, diagnosis and management*. New York: Raven Press, 1990;1985–1998, with permission.)

Concerns may arise about another activity that involves isometric exercise—sexual inter-minute course, which is accompanied by significant rises in pulse and BP (Nemec et al., 1976) (Table 6-5). The responses in ten healthy young men were essentially the same whether the man was on the top or on the bottom, despite the presumably greater isometric activity with the man-on-the-top position. Although actually quite rare even among patients with coronary disease, the triggering of myocardial infarction during sexual activity likely can be prevented by regular exercise (Muller et al., 1996).

	Rest	Intromission	Orgasm	2 min later
Blood pressure (mm Hg)				
Man on top	112/66	146/79	163/81	118/69
Man on bottom	113/70	143/74	161/77	121/71
Heart rate (bpm)				
Man on top	67	136	169	92
Man on bottom	65	125	163	77

bpm, beats per minute.
Adapted from Nemec ED, Mansfield L, Kennedy JW. Heart rate and blood pressure responses during sexual activity in normal males. Am Heart J 1976;92:274–277.

TABLE 6-5. *Blood pressure and pulse responses during sexual intercourse in ten normal men*

Mechanisms of Antihypertensive Effect

Exercise lowers BP through multiple mechanisms (Arakawa, 1993), including the following:

- Lower sympathetic nerve traffic accompanied by potentiation of the baroreceptor reflex (Grassi et al., 1994)
- Reduced arterial stiffness and increased total systemic arterial compliance (Tanaka et al., 2000)
- Increased release of endothelium-derived nitric oxide that may be related to lower plasma cholesterol (DeSouza et al., 2000)
- Increased insulin sensitivity (Araújo-Vilar et al., 1997)

Recommendations for Implementation

Without question, increased levels of physical activity either during ordinary life or with structured exercise will lower BP and prevent the onset of hypertension and diabetes, at least in part, through prevention of obesity (Schmitz et al., 2000), while at the same time protecting against osteoporosis and age-related declines in cardiovascular responsiveness (DeSouza et al., 2000).

Hypertensives may start with a reduced exercise capacity (Lim et al., 1996) and may experience additional difficulty if they take b-blockers, which blunt exercise-mediated increases in heart rate and cardiac output (Vanhees et al., 2000). Nonetheless, the hemodynamic responses to exercise can break through b-blockade, and a training effect can be achieved (Fahrenbach et al., 1995). Other antihypertensive agents should not interfere with exercise ability (Fahrenbach et al., 1995; Predel et al., 1996).

Despite the obvious benefits, few physicians counsel their patients about exercise (Leermakers et al., 2000), and most children perform less and less exercise, as physical education has largely been eliminated at schools and computers and television consume their out-of-school time (Rothstein, 2000). Obviously more attention must be directed at increasing physical activity both in hypertensives and in the population at large (Goran et al., 1999; Snell and Mitchell, 1999).

MODERATION OF ALCOHOL

Effects on Blood Pressure

Drinking of 60 g of ethanol, the amount con tained in five usual portions of beer (12 oz), wine (4 oz), or whiskey (1.5 oz), induces an immediate fall in BP averaging 4/4 mm Hg fol lowed, after 6 hours, by a rise averaging 7/4 mm Hg (Rosito et al., 1999). Although the apparent pressor effect may be exaggerated by a consid erable white-coat effect (i.e., higher readings in the office than by ambulatory monitoring) (Ryan and Howes, 2000), the BP does rise during heavy binge drinking (Seppä and Sillanaukee, 1999). Moreover, when heavy drinkers abstain, their BP usually goes down (Aguilera et al., 1999; Xin et al., 2001).

Beneficial Effects

On the other hand, overwhelming evidence sup-ports a protective effect of moderate, regular alcohol consumption of one-half to two portions per day on a host of cardiovascular and other diseases when compared to similar parameters in nondrinkers or heavy drinkers. Protection has been seen against total mortality (Grønbæk et al., 2000), coronary disease mortality (Gaziano et al., 2000), stroke (Rexrode et al., 2000), peripheral vascular disease (Djoussé et al., 2000), the incidence of type 2 diabetes (Wei et al., 2000), osteoporosis (Rapuri et al., 2000), and cancer mortality (Grønbæk et al., 2000). The survival benefit persists into old age (Simons et al., 2000), and the protection against coronary heart disease applies to diabetic men (Ajani et al., 2000) and women (Solomon et al., 2000) as well. These effects have been attributed to improvements in the lipid profile and in hemostatic factors, whereas the purported improvement in insulin sensitivity largely reflects a lower BMI and less central obesity among moderate drinkers (Bell et al., 2000).

Wine appears to be more protective than beer or whiskey (Renaud et al., 1999; Grønbæk et al., 2000), perhaps because it contains fewer nitrosamines (Berger, 1998) or more flavinoids and antioxidants. On the other hand, wine drinkers tend to have a healthier lifestyle (Tjønneland et al., 1999), so this apparent benefit may be exaggerated. Although there is a common perception that red wine is more protective than white wine, there is no evidence to support that conclusion.

Recommendations for Implementation

Beyond the obvious problems of alcohol abuse, which could become more common with any increase in average consumption in the population at large (Colhoun et al., 1997), there seems to be no reason to advise patients, hypertensive or not, to abstain from moderate alcohol consumption (i.e., one-half to two drinks per day). Whether those who do not drink should be advised of the many benefits observed with moderate drinking and thereby encouraged to begin drinking is a debatable issue. Some would encourage them to do so (Chafetz, 2000; Rimm, 2000); others would not (Goldberg et al., 2001), particularly those younger than 40 (Jackson and Beaglehole, 1995).

The following guidelines seem appropriate:

- Carefully assess alcohol intake, as some people drink well beyond moderate amounts without being aware of their excessive consumption or its deleterious effects.
- If intake is more than one portion per day in women or two per day in men, advise a reduction to that level. Women should be advised of an increase in the prevalence of breast cancer with more than one portion (10 g alcohol) per day (Smith-Warner et al., 1998).
- Strongly advise against binge drinking.
- For most people who consume moderate amounts of alcohol on a regular, daily basis, no change is needed.

OTHER DIETARY FACTORS

Although the evidence of an association between macronutrients and BP remains inconclusive (Preuss et al., 1996), the impressive results of the DASH diet (Fig. 6-2) strongly sup-port an antihypertensive effect of a diet low in fat and high in fiber and minerals (Sacks et al., 2001). Moreover, among more than 11,000 middle-aged men followed up for 6 years, BP was positively related to intake of saturated fatty acids, cholesterol, and starch and inversely related to intake of protein and the ratio of poly-unsaturated to saturated fatty acids (Stamler et al., 1996a).

Vegetarians tend to have low BP, but the reason for this is unknown (Burke and Beilin, 1994). When hypertensives consumed a vegetarian diet under controlled conditions for 6 weeks, an average fall in systolic BP of 5 mm Hg was observed (Margetts et al., 1988).

Fiber Intake

One feature of a vegetarian diet is the increased amount of fiber. A metaanalysis of all 12 randomized, controlled clinical trials published before July 1995 of the effect on BP of supplements of dietary fiber averaging 14 g per day found an average fall of 1.2/1.8 mm Hg (He et al., 1996). Fiber intake of less than 12 g per day was associated with a 1.57 increased relative risk for developing hypertension over a 4-year follow-up as compared to the risk associated with an intake of more than 24 g per day (Ascherio et al., 1992). The benefits found with increased fruits and vegetables in the DASH diet could reflect the increase in fiber from 9 to 31 g per day (Appel et al., 1997). Moreover, in the 12- to 14-year follow-up of the 75,000 women in the Nurses Health Study, the risk of stroke was significantly reduced by a higher intake of fruits and vegetables (Joshipura et al., 1999). The benefits of increased dietary fiber may reflect decreases in body weight and plasma insulin levels (Ludwig et al., 1999).

Dietary Fat Intake

In keeping with the potential contribution of the low saturated fat content of the DASH diet, other smaller studies have shown a lowering of BP with a low-fat diet (Rantala et al., 1997; Straznicky et al., 1999).

The type of fat may also be important. As a component of the cardiovascular beneficial Mediterranean diet (Visioli and Galli, 1998), olive oil may lower BP because of its high con-tent of monounsaturated fatty acids or antioxidant polyphenols (Ferrara et al., 2000). Higher intakes of the polyunsaturated linoleic acid may also lower BP (Grimsgaard et al., 1999) and reduce the incidence of hypertension (ZJ Zheng et al., 1999).

Lipid-Lowering Drugs

Beyond any antihypertensive effect, such lower-saturated-fat diets clearly protect against CVD (Mustad and Kris-Etherton, 2000). Both diet and lipid-lowering drugs, in particular statins (Yang et al., 2000), improve the endothelial dysfunction associated with dyslipidemia (Schneider et al., 2000), which may contribute to both the lower BP (Dormi et al., 2000) and the protection against atherosclerotic complications seen with lipid-lowering drugs (Maron et al., 2000).

Fish Oil and Omega-3-Polyunsaturated Fatty Acids

Similarly, both an antihypertensive effect (Mori et al., 2000) and a protective effect against stroke (Iso et al., 2001) have been seen with docosahexaenoic acid, one of the major omega-3-poly-unsaturated fatty acids (PUFA) in cold-water fish, confirming the beneficial effect of a diet of mackerel and herring reported by Singer et al. (1983). Two metaanalyses of controlled trials with fish oil supplements found significant antihypertensive effects of 3 to 6 g per day of omega-3-PUFA, averaging approximately a 4/3–mm Hg fall in BP among hypertensive patients (Appel et al., 1993; Morris et al., 1993). In a randomized, double-blind, 16-week controlled trial of 78 untreated hypertensives, those given 4 g per day of omega-3-PUFA had an average 3.8/2.0–mm Hg lower BP than did those given 4 g per day of corn oil (Toft et al., 1995). These effects may derive from improvements in endothelium-independent vasodilator mechanisms (Mori et al., 2000) and decreases in concentrations of soluble adhesion molecules (Miles et al., 2001).

Despite these beneficial effects, it is unlikely that such large amounts of fish oil supplements will be taken over long periods. Fortunately, just eating more fish reduces the risk for coronary disease, stroke, and all-cause mortality (J Zhang et al., 1999).

Protein Intake

Although high protein intake has been thought to be detrimental, in large part by placing an additional load on the kidney, the INTERSALT data showed a favorable effect: BPs averaged 3.0/2.5 mm Hg lower with a protein intake that was 30% higher than the mean as compared to an intake that was 30% lower than the mean (Stamler et al., 1996b). These data fit well with numerous observational studies from Japan and elsewhere that show an inverse relation between dietary protein and BP (Liu et al., 2000). How-ever, in the National Health and Nutrition Examination Survey III, increased dietary protein was positively associated with higher systolic BP (Hajjar et al., 2001). In a preliminary study, dietary supplements of L-arginine lowered BP, possibly by increasing synthesis of nitric oxide (Siani et al., 2000).

Carbohydrate Intake

The data are skimpy but intake of refined sugar tends to raise BP, whereas complex carbohydrates tend to lower BP (Preuss et al., 1996). High-carbohydrate diets may further raise plasma insulin, thereby interfering with the antihypertensive effect of weight reduction (Parillo et al., 1988).

Antioxidants

Vitamin C improves endothelial-dependent vasodilation (Taddei et al., 1998). Most cross-sectional data from diverse populations show an inverse relation between intake or plasma levels of vitamin C and BP (Ness et al., 1997). Supplements of vitamin C (500 mg per day) reduced systolic BP by 2.0 mm Hg in 40 older adults (Fotherby et al., 2000) and by 1.3 mm Hg in 45 middle-aged hypertensives (Duffy et al., 1999). In a carefully monitored trial of 68 normotensive men who were provided all of their food and drink, 1 month of a diet low in vitamin C was associated with a 0.8–mm Hg higher diastolic BP, and 1 month of a diet high in vitamin C with a 1.4–mm Hg lower diastolic BP (Block et al., 2001). The diastolic BP was inversely related to the plasma ascorbic acid level.

Vitamin E supplements do not appear to lower BP in treated hypertensives (Palumbo et al., 2000).

Caffeine

Acute Effects on Blood Pressure

Caffeine, consumed daily by approximately 80% of adults in coffee, tea, or cola drinks, acutely raises both systolic and diastolic BP from 5 to 15 mm Hg for several hours in some but not all subjects, more in hypertensives than normotensives (Rachima-Maoz et al., 1998). Tea may raise BP even more than would be expected from its caffeine content (Hodgson et al., 1999). The effect likely reflects vasoconstriction by antagonism of endogenous adenosine and increased arterial wave reflection (Vlachopoulos and O'Rourke, 2000). The pressor effect is exaggerated in hypertensives (Pincomb et al., 1996) and is additive to the pressor effect of nicotine (Narkiewicz et al., 1995).

This acute pressor effect has long been recognized but downplayed, mainly because tolerance rapidly develops so that less pressor effect occurs with repeated intake (Myers and Reeves, 1991). However, within 12 hours, tolerance is largely overcome, setting the stage for a significant pressor effect from the first morning cup of coffee (James, 1997). Although coffee consumption has been linked to an increased risk of coronary disease (James, 1997), most observational studies find little, if any, association (Kleemola et al., 2000; Sesso et al., 1999).

Chronic Effects on Blood Pressure

To assess the effects of repeated chronic caffeine intake, ambulatory BP monitoring has been performed on both normotensive and hypertensive subjects who consumed three to five cups of either caffeinated or decaffeinated coffee per day. Most of these studies find an increase in 24-hour BP of approximately 5/3 mm Hg in hypertensives and 2/1 mm Hg in normotensives with caffeinated coffee (Jee et al., 1999; Rakic et al., 1999).

Because responses may vary, it seems prudent to ask patients to test their own response by measuring home BP repeatedly during a week while consuming either their usual amount of caffeine-containing beverage or the same amount of decaffeinated beverage. If a significant pressor effect is seen, substitution of decaffeinated beverages should be recommended.

MISCELLANEOUS

Relaxation

In view of the evidence (more completely reviewed in Chapter 3) that stress-related anxiety (Jonas et al., 1997; Markovitz et al., 1993) and job strain (Pickering et al., 1996) may be involved in the development of hypertension, various stress-relieving techniques to lower BP have been used for many years (Jacobson, 1939). More recently, a variety of cognitive-behavioral therapies—including transcendental meditation, yoga, biofeedback, and psychotherapy—have been shown to reduce the BP of hypertensive patients at least transiently (Henderson et al., 1998). Although each therapy has its advocates, none has been shown conclusively to be either practical for the majority of hypertensives or effective in maintaining a significant long-term effect (Eisenberg et al., 1993; Hunyor et al., 1997). On the other hand, cognitive-behavioral therapy was found to reduce medication needs in hypertensive patients (Shapiro et al., 1997), and overall improvements in marital harmony have been associated with lower BP and reduction in left ventricular mass (Baker et al., 2000).

If available and acceptable to the patient, one or another form of relaxation therapy may be tried, as such techniques may provide additional benefits in reducing coronary risk beyond any effect on BP (Linden et al., 1996). Patients should be forewarned that short-term effects may not be maintained, so continued surveil-lance is needed.

Slow Breathing

Slow breathing guided by a device (Respi-Low, InterCure, Ltd., Neve Ilan, Israel) has been shown to reduce BP in hypertensives (Grossman et al., 2001; Rosenthal et al., 2001). Whether this provides more reduction in BP than other relaxation techniques is uncertain.

Bed Rest and Sedatives

When patients, even those whose disease is difficult to control on an outpatient basis, are hospitalized, their BP frequently comes down, mainly because the sympathetic nervous system becomes less active (Nishimura et al., 1987). This fall in BP may largely reflect the removal of the white-coat effect, as little change has been noted by repeated ambulatory monitoring (Fotherby et al., 1995).

The BP usually falls considerably during sleep. However, there is no evidence that sedatives or tranquilizers lower BP (U.S. Public Health Service Cooperative Study, 1965). Monoamine oxidase inhibitors will lower the BP, but their use is limited by the potential for bad pressor reactions with tyramine-containing foods.

Garlic and Herbal Remedies

Garlic, mainly as a deodorized powder, has been found to lower BP in a number of small, poorly controlled trials (Mashour et al., 1998).

Herbal remedies are being widely used for all sorts of unproved benefits, totally unsupervised in the United States because of congressional interference with the Food and Drug Administration's surveillance (Goldman, 2001). They are, at the least, better regulated elsewhere (Bauer, 2000). None has been shown to lower BP (with the obvious exceptions of *Rauwolfia* and *Veratrum*) and some, in fact, will raise BP, including *Ephedra* and licorice extract (Mansoor, 2001).

Other Modalities

Ultraviolet B irradiation has been claimed to lower BP (Krause et al., 1998). In a controlled study, *acupuncture* was of no benefit (Smith and Hess, 2000). *Pet owners* have demonstrated significantly lower systolic BPs and blood lipid levels than non–pet owners, effects not attributable to differences in obvious confounding factors (Anderson et al., 1992). They also have lesser BP rises in response to mental stress (Allen et al., 2001).

Surgical Procedures

From approximately 1935 through the 1950s, surgical sympathectomy, along with a rigid low-salt diet, was about all that was available for treating hypertension. Sympathectomy was shown to be beneficial for those with severe disease (Thorpe et al., 1950). With current medical therapy, there is no place for sympathectomy.

Neurovascular decompression has been used to remove presumed vascular compression of the left ventrolateral medulla since Jannetta et al. (1985) claimed relief of hypertension in 32 of 42 hypertensives by the procedure when it was per-formed for unrelated cranial nerve dysfunctions. Although hypertension in a few patients with neurologic manifestations of compression of the lateral medulla has been helped by decompression (Salvi et al., 2000), the majority of published series claiming success have been poorly documented and the patients followed up for only a short time (Geiger et al., 1998). Nonetheless, considerable evidence points to heightened sympathetic nervous activity in hypertensives with medullary compression (Gajjar et al., 2000; Morise et al., 2000). At the same time, carefully performed magnetic resonance imaging of the brainstem finds neurovascular contact in almost as many normotensives (16%) as hypertensives (23%) (Hohenbleicher et al., 2001). Hopefully, properly controlled trials will be done before surgical decompression is more widely used.

CONCLUSIONS

The various lifestyle modifications discussed in this chapter will reduce the BP of most hypertensives, in some to a level that is safe enough to obviate drug therapy. One or more of these life-style modifications should be tried in all patients. Those with mild hypertension may thereby be able to stay off drugs; those with more severe hypertension may need less medication.

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7
Treatment of Hypertension: Drug Therapy

In the previous two chapters, I reviewed the evidence for the need for blood pressure (BP) reduction and the use of lifestyle modifications to lower the BP. This chapter provides ways to improve on the currently inadequate control of the disease. Then each class of drugs currently available is described. An analysis of initial drug choice and of the subsequent order of additional therapy follows; then come considerations of the management of special populations and of hypertensives with various other conditions.

BACKGROUND

Because the treatment of hypertension is among the leading indications for the use of drugs, new agents constantly are being introduced and heavily promoted. The choice of drugs is one of the factors that affects the efficacy of therapy (Mar and Rodríguez-Artalejo, 2001), but choices are often based on promotional activities that may be biased (Ziegler et al., 1995). In this chapter, I constantly attempt to maintain an objective view, both about the use of drugs overall and about the relative value of individual agents. Specific choices are often favored, in keeping with the recent guidelines from multiple expert committees (Feldman et al., 1999; Guidelines Subcommittee, 1999; Joint National Committee, 1997; Ramsay et al., 1999).

As we shall see, currently available antihypertensive drugs, hopefully used in concert with appropriate lifestyle modifications, can control the BP in most hypertensives (Black et al., 2001). Yet, in every survey, in only a minority of patients is the BP lower than 140/90 mm Hg, the usual criterion for control. Therefore, before considering the drugs that are available and their indications, the issue of how to achieve better overall control of hypertension will be addressed.

CURRENT STATE OF CONTROL OF HYPERTENSION

Inadequate rates of control have been reported in representative samples of the population from countries all over the world (Erdine, 2000; Fuentes et al., 2000; Lloyd-Jones et al., 2000), as well as from patients being seen in various health care settings (Alexander et al., 1999; Berlowitz et al., 1998; Cuspidi et al., 1999).

Particularly instructive are data from the participants in the longer than 50-year Framingham Heart Study, who are likely to be as aware of both the presence of hypertension and the need for its control as any group of people in the world. Among the entire 10,333 participants, of whom approximately 40% were hypertensive, the rate of use of antihypertensive medications increased from 2.3% to 24.6% in men and from 5.7% to 27.7% in women from 1950 to 1989 (Mosterd et al., 1999). These figures would translate into therapy being used by more than half of those with hypertension. As a consequence, the prevalence of BP higher than 160/ 100 mm Hg declined significantly. However, in the same group of hypertensives, the goal of therapy, a BP of less than 140/90 mm Hg, was reached by only 29% (Lloyd-Jones et al., 2000).

These figures are remarkably similar to those reported from the third survey of a representative sample of the entire U.S. population, the National Health and Nutrition Examination Survey (Joint National Committee, 1997).

Reasons for Poor Control

The reasons for poor control are multiple, including these:

- As many as a third of hypertensives remain unaware of the diagnosis, largely reflecting the asymptomatic nature of the condition.
- Many patients do not take their prescribed medications. In most surveys, as many as one-half to a one-fourth of patients started on anti-hypertensive drugs will have stopped taking them within a year (Caro et al., 1999; McInnes, 1999).
- Many physicians do not prescribe enough medication to control their patients' hypertension. Although blame is usually directed at patients, in virtually every survey twice as many patients are taking medications as are being controlled, indicating that patients are willing but their physicians are not prescribing them what they need. This physician “noncompliance” has been recently documented among primary care physicians in the United States (Oliveria et al., 2000), in the United Kingdom (Swales, 1999), in France (Lang et al., 2001), and in five U.S. Veterans Affairs (VA) clinics (Berlowitz et al., 1998). As seen in most surveys, only about 25% of the VA patients were well controlled. As Berlowitz et al. (1998) noted:

> Poor control of blood pressure could not be explained by a lack of access to medical care. Our patients were regular users of health care, averaging more than five medical-clinic visits with a blood-pressure measurement per year. Medications for patients who are treated at Veterans Affairs hospitals are either free or available for a small copayment. . . . In our study, physicians frequently failed to increase the dose of antihypertensive medications or to try new treatments in patients with elevated blood pressure. Overall, antihypertensive medications were increased at 6.7 percent of hypertension-related visits. Among visits in which diastolic blood pressure of ³90 mm Hg and systolic blood pressure of ³155 mm Hg were recorded, the frequency of increases in antihypertensive medications was 25.6 percent. At visits in which a diastolic blood pressure of <90 mm Hg and a systolic blood pressure of ³165 mm Hg were recorded, the frequency was 21.6 percent. Thus, for about three-quarters of visits in which elevated blood pressures were recorded, physicians did not increase medications.

Fortunately, the VA has taken steps to improve the situation. Specifically, a single computerized record system that provides instant feedback has increased the percentage of controlled hypertension from 29% to 40% in 16 months (Fletcher et al., 2001).

The Patient's Problems

Obviously, physicians and their assistants must be willing to provide whatever therapy is needed to control hypertension. However, the patient is the most critical element in the success or failure of therapy. The most careful physician prescribing the most effective therapy will not control hypertension unless the patient is willing and able to take the pills and modify their lifestyle as needed.

Hypertensives have special problems related to the nature of their disease. Many are largely unaware of the definition, possible causes, sequelae, and therapeutic needs of hypertension. Being asymptomatic, patients may have little motivation to seek or follow treatment. Many are found to have high BP at the age (late thirties and early forties) when the threat of a loss of vigor and vitality is insidiously beginning, and the recognition of hypertension often provokes a strong denial reaction. Moreover, the diagnosis carries considerable economic and social threats—loss of job, insurance, and sexual potency—that may further inhibit people from accepting the diagnosis and dealing with the problem. If further depressed over the diagnosis, patients may be even more unwilling to take medications (DiMatteo et al., 2000).

Additional barriers may preclude long-term management in the steadily increasing number of uninsured people in the United States who often receive only episodic care at public hospitals and who may not be able to afford their medications (Ahluwalia et al., 1997; Tamblyn et al., 2001).

Moreover, the therapy for hypertension has all the wrong characteristics for compliance, and these are often compounded by clinical practices such as the use of

multiple daily doses of medications (Payne and Esmonde-White, 2000). Side effects discourage adherence. As with impotence in the use of diuretics (Grimm et al., 1997), the symptoms that follow institution of drug therapy may not be expected from the known pharmacologic effects of the drug.

Assessment of Pill Taking

Although there are multiple ways to assess the degree of patients' pill taking, none has been found to be particularly accurate (Choo et al., 1999). Just asking the patient in a nonthreatening way (e.g., “Patients often have difficulty in taking their pills. Have you missed taking any of yours?”) is often productive. More sophisticated techniques, such as electronic medication monitors, are available and may be helpful in clinical practice (Burnier et al., 2001). Such monitors have shown that some patients omit drugs over weekends, increase doses before office visits, and often miss a dose (Steiner and Earnest, 2000).

Ways to Improve Pill Taking

In their review of more than 1,500 citations about ways to improve pill taking, Haynes et al. (1996) concluded that

> The interventions that were effective were complex, including various combinations of more convenient care, information, counseling, reminders, self-monitoring, reinforcement, family therapy, and other forms of additional supervision or attention. Even the most effective interventions did not lead to substantial improvements in adherence. It is time that additional efforts be directed towards developing and testing innovative approaches to assist patients to follow treatment prescriptions.

A similarly critical review concluded, “the methodological quality of many trials [of interventions to increase compliance] was less than optimal, prohibiting strong recommendations” (Newell et al., 1999). Nonetheless, reasonable and likely helpful ways to increase maintenance of therapy are available (Freis, 1999; Miller et al., 1997), as summarized in Table 7-1. A few deserve additional comment:

TABLE 7-1. *Guidelines to improve maintenance of antihypertensive therapy*

- As compared to physicians, nurses using detailed clinical protocols can provide more efficient follow-up care (DeBusk et al., 1999; Hill and Miller, 1996) with comparable patient outcomes (Mundinger et al., 2000).
- To reduce costs, the minimum effective doses should be prescribed, generic brands should be used, and larger doses of tablets that are not specially designed for slow release should be broken in half with readily available pill cutters.
- More and more once-a-day formulations are available so that fewer tablets are needed.
- Medications will hopefully be provided in calendar blister packs, the use of which has been shown to improve the control of hypertension (Simmons et al., 2000).

The use of less-expensive medications is being emphasized in an attempt to reduce the costs of health care and to ensure that the uninsured indigent are not denied needed medications whenever there is no safety net in place to ensure care for the poor. Although the indigent can often be provided medications through pharmaceutical company programs (Dustan et al., 1992), the cost of therapy remains a barrier to the management of hypertension (Tamblyn et al., 2001).

On the other hand, simplistic comparisons of costs based purely on the costs per tablet may be misleading. For example, in a survey of hypertensive patients in South Carolina, the experiences of 947 who were given three 60-mg doses of short-acting generic diltiazem per day were compared to the experiences of 301 given one 180-mg dose of the more expensive brand of long-acting diltiazem per day (Sclar et al., 1994). Those on the once-a-day dose required fewer concomitant antihypertensive drugs, adhered more closely to therapy, and required less use of and expenditures for physician and hospital services. Although their drug costs were higher, their total costs of health care were lower.

Before considering the roles of individual drugs and the manner in which they are used in improving the overall management of hypertension, a detailed description of the various choices will be provided.

SPECIFICS ABOUT ANTIHYPERTENSIVE DRUGS

The modern era of antihypertensive therapy began only slightly more than 40 years ago with the pioneering work of Ed Freis in the United States and Horace Smirk in New Zealand (Piepho and Beal, 2000). Since then, a large panoply of drugs have been developed, as listed in Table 7-2. We will consider the drugs in the order shown in Table 7-2. Some that are used extensively else-where but that are not now available in the United States will also be covered, along with newer agents that are on the horizon. Drugs that have outlived their usefulness will be disregarded.

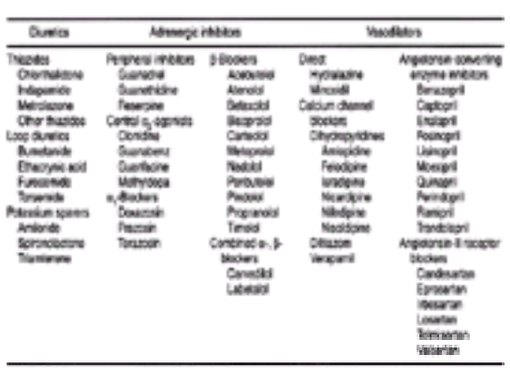


TABLE 7-2. *Antihypertensive drugs available in the United States (as of 2001)*

It is of interest to notice the changes in the relative frequency of use of the major drug classes in the United States from 1986 through 2000 (Fig. 7-1). In particular, the use of the newer classes—angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and calcium channel blockers (CCBs)—has rapidly risen. The reasons for these changes should become obvious in the remainder of this chapter.

After a description of some of the basic pharmacology and clinical usefulness of each agent, we will consider the choice of first and second drugs, the selection of specific drugs for various types of hypertensive patients, the use of combinations, and conditions wherein special care is advised in the choice of drugs. The use of drugs in various secondary forms of hypertension (e.g., ACEIs in renovascular hypertension; spironolactone in primary aldosteronism) is considered in the respective

chapters on these secondary states.

DIURETICS

As seen in Figure 7-1, diuretics are once again the most frequently prescribed drugs for treating hypertension, after a period when their use declined. This reversal reflects the recognition of their ability, in lower doses, to provide excellent protection against heart attacks, heart failure, and strokes, protection equal to that seen with ACEIs or CCBs (Blood Pressure Lowering, 2000).

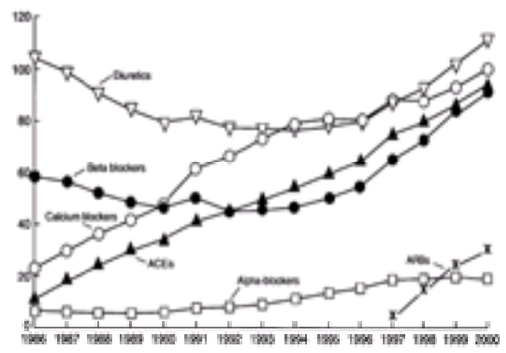


FIG. 7-1. Numbers of prescriptions (in millions) for antihypertensive drugs dispensed in retail channels in the United States from 1986 to 2000. ACEIs, angiotensinconverting enzyme inhibitors; ARBs, angiotensin II–receptor blockers. (Reprinted from IMS Health. National Prescription Audit. Ambler, PA: IMS America, Ltd, 2000, with permission.)

As noted earlier, in a world increasingly concerned about the costs of health care, diuretics may also be advocated because, purely on the basis of cost per tablet, they are much cheaper (Siegel et al., 2001).

Classification

Diuretics differ in structure and major site of action within the nephron (Fig. 7-2). The site of action determines their relative efficacy, as expressed in the maximal percentage of filtered sodium chloride excreted (Brater, 2000). Agents acting in the proximal tubule (site I) are seldom used to treat hypertension. Treatment is usually initiated with a thiazide-type diuretic (acting at site III, the distal convoluted tubule). Chlorthalidone and indapamide are structurally different from, although still related to, the thiazides and will be covered with them. If renal function is significantly impaired (i.e., serum creatinine exceeds 1.5 mg per dL), a loop diuretic (acting at site II, the thick ascending limb of the loop of Henle) or metolazone likely will be needed. A potassium-sparing agent (acting at site IV) may be given with the diuretic to reduce the likelihood of hypokalemia. By themselves, potassium-sparing agents are relatively weak antihypertensives. The molecular mechanisms by which these various diuretics act on tubular transporters controlled by individual genes have been reviewed by Hebert (1999).

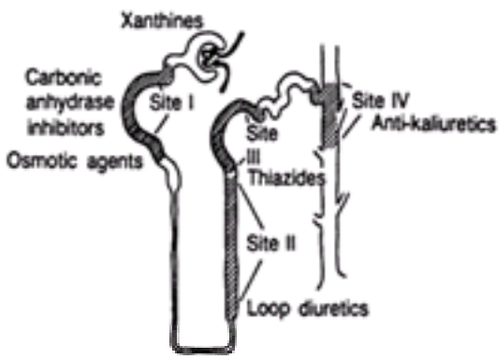
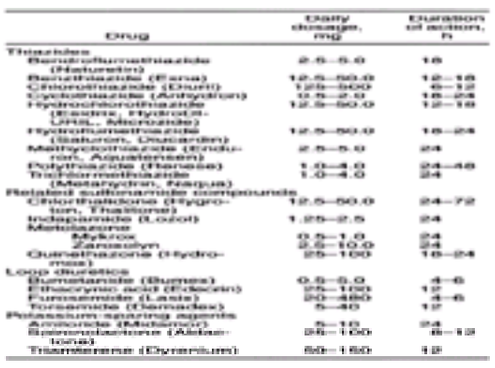


FIG. 7-2. Diagrammatic representation of the nephron showing the four main tubular sites where diuretics interfere with sodium reabsorption. [Reprinted from Lant A. Diuretic drugs. Progress in clinical pharmacology. *Drugs* 1986; 31(Suppl 4):40–55, with permission.]

The specific agents now available in the United States are listed in Table 7-3.



Drug	Daily dosage, mg	Duration of action, h
Thiazides		
Bendroflumethiazide (Naturetin)	2.5–5.0	18
Benzthiazide (Exna)	12.5–50.0	12–18
Chlorothiazide (Diuril)	125–500	6–12
Cyclothiazide (Anhydron)	1.5–2.0	18–24
Hydrochlorothiazide (Esidrix, Hydrodiuril, Oretic, Microzide)	12.5–50.0	12–18
Hydroflumethiazide (Saluron, Diucardin)	12.5–50.0	18–24
Methyclothiazide (Enduron, Aquatensen)	2.5–5.0	24
Polythiazide (Renese)	1.0–4.0	24–48
Trichlormethiazide (Metahydrin, Naqua)	1.0–4.0	24
Related sulfonamide compounds		
Chlorthalidone (Hygroton, Thalitone)	12.5–50.0	24–72
Indapamide (Lozol)	1.25–2.5	24
Metolazone		
Mykrox	0.5–1.0	24
Zaroxolyn	2.5–10.0	24
Quinethazone (Hydromox)	25–100	18–24
Loop diuretics		
Bumetanide (Bumex)	0.5–5.0	4–6
Ethacrynic acid (Edecrin)	25–100	12
Furosemide (Lasix)	20–480	4–6
Torsemide (Demadex)	5–40	12
Potassium-sparing agents		
Amiloride (Midamor)	5–10	24
Spironolactone (Aldactone)	25–100	8–12
Triamterene (Dyrenium)	50–100	12

TABLE 7-3. *Diuretics and potassium-sparing agents (U.S. trade names)*

Thiazide Diuretics

Mode of Action

The thiazide diuretics act by inhibiting sodium and chloride cotransport across the luminal membrane of the early segment of the distal convoluted tubule, where 5% to 8% of filtered sodium is normally reabsorbed (Puschett, 2000; Reyes and Taylor, 1999) (Fig. 7-2, site III). Plasma and extracellular fluid volume are thereby shrunken, and cardiac output falls (Wilson and Freis, 1959). Humoral and intrarenal counterregulatory mechanisms rapidly reestablish the steady state so that sodium intake and excretion are balanced within 3 to 9 days in the presence of a decreased body fluid volume (Puschett, 2000). With chronic use, plasma volume returns partially toward normal but, at the same time, peripheral resistance decreases (Conway and Lauwers, 1960) (Fig. 7-3). The fall in resistance may reflect a vasorelaxant effect as seen *in vitro* (Colas et al., 2001).

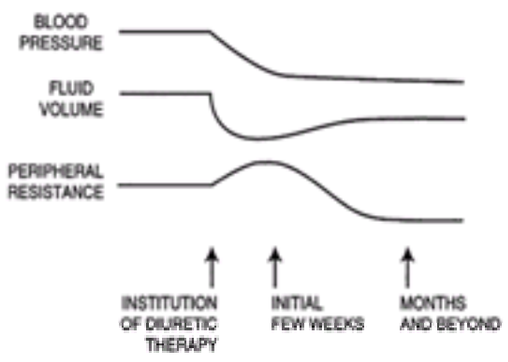


FIG. 7-3. Scheme of the hemodynamic changes responsible for the antihypertensive effects of diuretic therapy.

Determinants of Response

The degree of BP response to diuretics is predicated on their capacity to activate the counterregulatory defenses to a lower BP and a shrunken fluid volume—in particular, a reactive rise in renin and aldosterone levels. Those who start with low, suppressed plasma renin activity (PRA) levels and who are capable of mounting only a weak rise in these levels after diuretics are initiated have been shown to be more "diuretic-responsive" (Niarchos et al., 1984). Those who respond less well, with a fall in mean BP of less than 10%, were found to have a greater degree of plasma volume depletion and greater stimulation of renin and aldosterone, contributing to a persistently high peripheral resistance (van Brummelen et al., 1980). Blockage of the reactive rise in renin-angiotensin-aldosterone, as with the addition of an ACEI, will potentiate the antihypertensive action (Radevski et al., 2000).

The presence of a polymorphism of the G-protein b_3-subunit that has been noted to be more common in patients with low-renin, volume-mediated hypertension has also been found to be associated with greater BP responsiveness to a thiazide diuretic (Turner et al., 2001).

Thiazide Congeners

Indapamide

Indapamide (Lozol) is also a chlorobenzene sulfonamide but has a methylindoline moiety, which may provide additional antihypertensive actions beyond its diuretic effect by inhibiting calcium entry into vascular smooth muscle cells (Zempel et al., 1997). It is as effective in reducing the BP as are thiazides or CCBs (Emeriau et al., 2001); maintains a 24-hour effect; and, in appropriately low doses of 1.25 mg per day, rarely raises serum lipids (Hall et al., 1994). With 1.5-mg doses, regression of left ventricular hypertrophy (LVH) was better than with enalapril, 20 mg per day (Gosse et al., 2000). In a small group of patients with moderate renal insufficiency, indapamide preserved renal function better than did hydrochlorothiazide (HCTZ) (Madkour et al., 1995). On the background of an ACEI, indapamide provided a 43% reduction in recurrences of stroke (PROGRESS Collaborative Group, 2001).

Metolazone

Metolazone, a long-acting and more potent quinazoline thiazide derivative, maintains its effect in the presence of renal insufficiency (Paton and Kane, 1977). Small doses, 0.5 to 1.0 mg per day, of a new formulation (Mykrox) may be equal to ordinary long-acting thiazide diuretics (Miller et al., 1988); the agent is particularly useful in patients with renal insufficiency and resistant hypertension.

Efficacy of Thiazides

When used alone, thiazide diuretics provide efficacy similar to that of other classes of drugs (Neaton et al., 1993). Blacks and the elderly respond better to diuretics than do nonblacks and younger patients (Materson et al., 1993).

Diuretics potentiate the effect of all other antihypertensive agents, including CCBs (Burris et al., 1990). This potentiation depends on the contraction of fluid volume by the diuretic (Finnerty et al., 1970) and the prevention of fluid accumulation that frequently follows the use of other antihypertensive drugs. Because of the altered pressurenatriuresis curve of primary hypertension (Saito and Kimura, 1996), whenever the BP is lowered, fluid retention is expected (Fig. 7-4). The need for a diuretic may be lessened with ACEIs and angiotensin II–receptor blockers (ARBs), which inhibit the renin-aldosterone mechanism, and with CCBs, which have some intrinsic natriuretic activity.

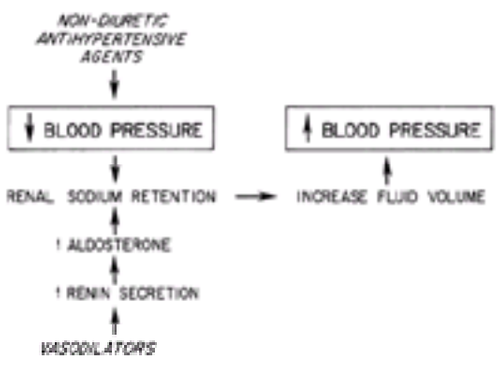


FIG. 7-4. Manner by which nondiuretic antihypertensive agents may lose their effectiveness by reactive renal sodium retention.

Duration of Action

The durations of action listed in Table 7-3 relate to the diuretic effect; the antihypertensive effect lasts beyond the diuretic effect. HCTZ once daily persistently reduced BP after 24 hours (Lacourcière and Provencher, 1989). HCTZ, 25 mg, at 7:00 a.m. for 4 weeks, converted hypertensives whose BP did not fall during the night, or nondippers, into dippers, further documenting the duration of antihypertensive effect (Uzu and Kimura, 1999). Bendrofluazide maintains its efficacy for 48 hours (Girvin and Johnston, 1998).

Dosage

Monotherapy

The recommended daily dose of thiazide diuretics has been progressively falling from as high as 200 mg HCTZ or equivalent doses of other thiazides in the early 1960s (Cranston et al., 1963) to as little as 6.25 to 12.50 mg today.

In hypertensives with good renal function, most of the antihypertensive effect will be obtained from such small doses, with less hypokalemia and other side effects (Carlsen et al., 1990; Harper et al., 1994; Johnston et al., 1991). Flack and Cushman (1996) have summarized the evidence that 12.5 mg HCTZ effectively lowers BP,

in most studies comparable to 25.0- to 50.0-mg doses.

In the massive Systolic Hypertension in the Elderly Program (SHEP) (SHEP Cooperative Research Group, 1991), 12.5 mg chlorthalidone was the starting dose and was adequate to bring the systolic BPs down to the goal in almost half of the subjects.

Even though most patients will have a good response to such small doses, some patients will require more, even up to 200 mg HCTZ per day (Freis et al., 1988). In another study, 12.5 mg HCTZ did not lower BP over a 4-week interval, but 25.0 mg did thereafter (Borghi et al., 1992). However, as shown by Carlsen et al. (1990), the full antihypertensive effect of low doses of diuretic may not become apparent in 4 weeks, so patience is advised when low doses are prescribed.

Combination Therapy

Even more convincing data confirm a significant effect from small doses, even below 12.5 mg per day HCTZ, when diuretics are added to a variety of other drugs to enhance their antihypertensive efficacy. This was most clearly documented with the combination of 6.25 mg HCTZ plus the b-blocker bisoprolol (Frishman et al., 1994). Similar potentiation of ACEI efficacy with 6.25 mg HCTZ has been seen (Andrén et al., 1983).

Thiazides may also be coupled with loop diuretics in those with renal impairment, because they counter the distal nephron hypertrophy that occurs with loop diuretics alone (Brater, 2000).

Conclusion

The overall evidence indicates that most hypertensives will respond over time to small doses of thiazide diuretic (i.e., 12.5–25.0 mg HCTZ) and that the relatively little additional effect that will be achieved by raising the daily dose beyond 25 mg per day comes at a high price in terms of side effects. In combinations, even 6.25 mg may be enough.

Resistance to Diuretics

Resistance to the natriuretic and antihypertensive action of diuretics may occur for numerous reasons (Ellison, 1999):

- Excessive dietary sodium intake may over-whelm the diuretic's ability to maintain a shrunken fluid volume (Winer, 1961).
- For those with renal impairment (i.e., serum creatinine >1.5 mg per dL or creatinine clearance <30 mL per minute), thiazides likely will not work; because these drugs must be secreted into the renal tubules to work and because endogenous organic acids that build up in renal insufficiency compete with diuretics for transport into the proximal tubule, the renal response progressively falls with increasing renal damage (see Chapter 9).
- Food affects the absorption and bioavailability of different diuretics to variable degrees (Neuvonen and Kivistö, 1989), so the drugs should be taken in a uniform pattern in terms of the time of day and food ingestion.
- Nonsteroidal antiinflammatory drugs (NSAIDs) may blunt the effect of most diuretics (Johnson, 1998).

Side Effects

As shown in Figure 7-5, the likely pathogenesis for most of the more common complications related to diuretic use arises from the intrinsic activity of the drugs, and most complications are, therefore, related to the dose and duration of diuretic use. Logically, side effects occur with about the same frequency and severity with equipotent doses of all diuretics, and their occurrence will diminish with lower doses. In general, the longer the diuretic action, the more common the various complications: Hypokalemia was three times more common with the longer-acting chlorthalidone than with HCTZ in the Multiple Risk Factor Intervention Trial (Grimm et al., 1985).

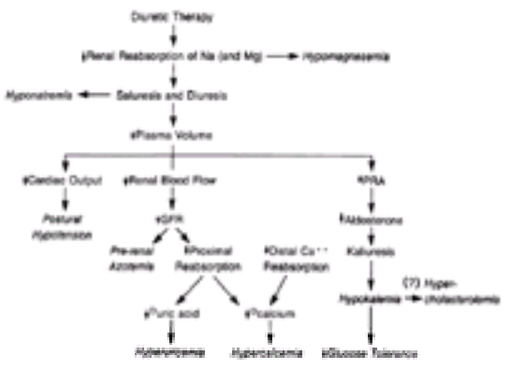


FIG. 7-5. Mechanisms by which chronic diuretic therapy may lead to various complications. The mechanism for hypercholesterolemia remains in question, although it is shown as arising via hypokalemia. Ca, calcium; Cl, chlorine; GFR, glomerular filtration rate; Na, sodium; Mg, magnesium; PRA, plasma renin activity.

Hypokalemia

As thiazides inhibit the coupled reabsorption of Na^+/Cl^- in the early distal convoluted tubule, increased urinary K^+ loss may occur for multiple reasons: increased flow-dependent K^+ secretion in the distal nephron; volume contraction that activates release of both vasopressin and reninaldosterone; and diuretic-induced hypochloremic metabolic alkalosis, which, in turn, redistributes K^+ into cells, leading to a further decrease in serum K^+ (Wilcox, 1999).

Magnitude. The degree of hypokalemia is dose dependent. With traditional, higher doses (50–100 mg HCTZ), the fall in serum potassium ranged from 0.1 to 1.4 mmol per L, averaging approximately 0.7 mmol per L (Grobbee and Hoes, 1995). With 25 mg HCTZ, the fall has ranged from 0.2 to 0.7 mmol per L, whereas with 12.5 mg HCTZ, no fall to as much as a 0.3-mm per L fall has been reported (Weir et al., 1996a).

These falls translate to an incidence of hypokalemia (<3.5 mmol per L) of approximately 20% on higher doses (Widmer et al., 1995) and perhaps 5% to 10% on 12.5 to 25.0 mg per day of HCTZ or chlorthalidone (Franse et al., 2000b). Diuretic-induced hypokalemia will be accentuated by increased amounts of sodium intake (Ram et al., 1981) and in those with lower total body potassium stores, including many elderly patients (Flynn et al., 1989).

Consequences. Most of the overt hazards of diuretic-induced hypokalemia have been seen only with fairly marked potassium depletion (Knochel, 1984), although muscle weakness, polyuria, and a propensity toward arrhythmias may appear with relatively mild hypokalemia. Patients on digitalis may develop toxicity, perhaps because both digitalis and hypokalemia inhibit the Na^+/K^+–adenosine triphosphatase (Na^+/K^+-ATPase) pump, the activity of which is essential to normal intracellular electrolyte balance and membrane potential (Nørgaard and Kjeldsen, 1991).

Ventricular Arrhythmias and Sudden Death. There appears to be a dose-dependent increase in sudden death with non–potassium-sparing (naked) diuretics (Grobbee and Hoes, 1995). In two case-control studies, the risk of sudden death was nearly doubled in those on large doses of naked diuretics as compared to those on thiazide plus a potassium-sparing agent (Hoes et al., 1995; Siscovick et al., 1994). In the SHEP trial, among those randomly allocated to 12.5 to 25.0 mg chlorthalidone, the 7.2% who developed hypokalemia had less than half the reduction in major cardiovascular events than those who remained normokalemic (Franse et al., 2000b). In the Studies of Left Ventricular Dysfunction trial, use of a non– potassium-sparing diuretic was associated with a 37% increased risk of arrhythmic death as compared to use of a potassium-sparing diuretic (HA Cooper et al., 1999).

The problem may be greatest for hypertensives who undergo major stress, particularly if they have underlying LVH, which is associated with an increased frequency of complex ventricular arrhythmias (James and Jones, 1991). During stress, b_2-receptor-mediated activation of the Na^+/K^+-ATPase pump causes potassium to enter

cells. Therefore, the presence of prior diuretic-induced hypokalemia will increase the likelihood of more severe hypokalemia appearing during stress or the use of b_2-agonists (Lipworth et al., 1990). Prevention of such b-receptor-mediated shifts of potassium could explain much of the protection against mortality in patients given nonselective b-blocker drugs after an acute myocardial infarction (MI).

Effect on Blood Pressure. Hypokalemia can set off various processes that can raise the BP (Linas et al., 1988), including a worsening of insulin resistance (Langford et al., 1990). Dietary potassium depletion has been found to raise the BP (Krishna et al., 1989), whereas the correction of diuretic-induced hypokalemia lowered the mean BP by an average of 5.5 mm Hg in a group of 16 hypertensives on a constant dose of diuretic (Kaplan et al., 1985).

Prevention of Diuretic-Induced Hypokalemia. Prevention is preferable. By lowering dietary sodium, increasing dietary potassium, and using the least amount of diuretic needed, potassium depletion may be avoided. A lower dietary sodium intake (72 mmol per day) reduced diuretic-induced potassium loss by half of that observed on a higher sodium intake (195 mmol per day) (Ram et al., 1981). A potassium-sparing agent, b-blocker, or ACEI given with the diuretic will reduce the degree of potassium loss (Nader et al., 1988) but may not prevent the development of hypokalemia (Sawyer and Gabriel, 1988).

Repletion of Diuretic-Induced Hypokalemia. If prevention does not work, the potassium deficiency can be replaced with supplemental K^+, preferably given as the chloride; other anions (as found in most fruits rich in potassium) will not correct the alkalosis or the intracellular K^+ deficiency as well (Kopyt et al., 1985). However, potassium citrate (Sakhaee et al., 1991) or bicarbonate (Frassetto et al., 2000) will be more effective in reducing urinary calcium loss in patients with renal stones or osteoporosis. Microencapsulated forms of KCl are more acceptable to patients than the various liquid preparations and have been found to cause fewer upper gastrointestinal mucosal lesions than the wax-matrix form (Hutcheon et al., 1988). The KCl may be given as a potassium-containing salt substitute; a number of these substitutes are available, and they are less expensive than potassium supplements.

If the patient is continued on the thiazide, 40 mmol per day of supplemental potassium or the addition of a potassium-sparing agent will usually overcome hypokalemia (Schnaper et al., 1989). Concomitant hypomagnesemia will also be corrected with the potassium sparer.

Caution is advised in giving potassium supplements to patients receiving ACEIs or ARBs whose aldosterone levels are suppressed and who may be unable to excrete extra potassium. The problem may be compounded in diabetics who may be unable to move potassium rapidly into cells and in those with renal insufficiency who may have a limited ability to excrete potassium.

Hypomagnesemia

Some of the problems attributed to hypokalemia may be caused by hypomagnesemia instead, and potassium repletion may not be possible in the presence of magnesium depletion (Whang et al., 1985).

Although loop diuretics tend to cause more urinary magnesium loss than do thiazides, hypomagnesemia and significant cellular depletion may occur with large doses of either (Dørup et al., 1993). However, conventional doses of diuretics rarely induce magnesium deficiency (Wilcox, 1999).

Clinical features include weakness, nausea, neuromuscular irritability, and the appearance of ventricular arrhythmias, which are resistant to treatment unless both hypomagnesemia and hypokalemia are corrected (Whang et al., 1985).

Magnesium wastage is lessened by use of smaller doses of diuretics and concomitant use of a potassium-sparing agent (Schnaper et al., 1989). If repletion is needed, oral magnesium oxide, 200 to 400 mg per day (10 to 20 mmol), or potassium-magnesium citrate may be tolerated without gastrointestinal distress (Pak, 2000).

Hyperuricemia

Serum uric acid levels are high in as many as 30% of untreated hypertensives and may independently predict cardiovascular events (Franse et al., 2000a). Thiazide therapy increases the incidence of hyperuricemia and may provoke gout, with an annual incidence of 4.9% at levels above 9 mg per dL (Campion et al., 1987). In the Hypertension Detection and Follow-Up Program, diuretic-induced rises in uric acid were rarely followed by gout (15 episodes over 5 years among 3,693 subjects) and were not associated with loss of renal function or mortality (Langford et al., 1987).

Thiazide-induced hyperuricemia need not be treated until a kidney stone or gout appears (Dykman et al., 1987). If therapy is given, the logical choice is probenecid to increase renal excretion of uric acid. Only in patients who are hyperuricemic from excessive uric acid production, unrelated to diuretic use, should allopurinol be used, because it may cause serious toxicity (Dykman et al., 1987).

Calcium Metabolism Alterations

Renal calcium reabsorption also is increased with chronic thiazide therapy, and urinary calcium excretion is decreased by 40% to 50% (Friedman and Bushinsky, 1999). A slight rise in serum calcium (i.e., 0.1–0.2 mg per dL) is usual, and hypercalcemia is often provoked in patients with preexisting hyperparathyroidism or vitamin D– treated hypoparathyroidism. The fact that serum calcium levels do not continue to rise in the face of reduced calcium excretion likely reflects the combination of reduced intestinal absorption of calcium (Sakhaee et al., 1984) and retention of calcium in bone (Rejnmark et al., 2001). The former effect likely reflects a suppression of parathyroid hormone and vitamin D synthesis from the slight hypercalcemia and makes thiazide therapy a practical way to treat patients with renal stones caused by hypercalcemia from increased calcium absorption (Quereda et al., 1996). The retention of calcium in bone offers protection from osteoporosis and fractures (LaCroix et al., 2000).

Hyperlipidemia

In their metaanalysis of all controlled and uncontrolled clinical trials published from 1966 through 1993, Kasiske et al. (1995) found that diuretics given in doses greater than the equivalent of 50 mg HCTZ induced these statistically significant changes (in millimoles per liter): total cholesterol, a 0.12 increase; low-density lipoprotein (LDL) cholesterol, a 0.19 increase; and triglycerides, a 0.10 increase. There was no significant change in high-density lipoprotein (HDL) cholesterol. In this analysis, cholesterol levels tended to decrease with time in both treated and untreated groups, whereas the effects of diuretics on triglycerides were seen only in short-term studies.

With currently used lower doses, thiazides induce minimal, if any, adverse changes in the lipid profile (Lakshman et al., 1999; Weir and Moser, 2000). It may still be useful to monitor lipid levels after a few months of thiazide use and, if elevated, to encourage a low-saturated-fat diet.

Glucose Intolerance and Insulin Resistance

Insulin resistance (Lithell, 1996), impairment of glucose tolerance, precipitation of overt diabetes (Samuelsson et al., 1996), and worsening of diabetic control (Goldner et al., 1960) have all been observed in patients taking thiazides. Rarely, diuretics may precipitate hyperosmolar, nonketotic diabetic coma (Fonseca and Phear, 1982). As with all the adverse effects of diuretics, the impairment of glucose utilization that connotes insulin resistance is seen more with high doses and less (or not at all) with therapeutically effective lower doses (equivalent to 12.5 mg HCTZ) (Harper et al., 1995).

With currently used lower doses, no increase in the incidence of diabetes was noted in a prospective cohort study (Gress et al., 2000). Moreover, in the SHEP trial, the elderly, non– insulin-dependent diabetics given low-dose chlorthalidone had the same 34% reduction in cardiovascular disease rate (as compared to the placebo-treated subjects) as did the nondiabetic patients (Curb et al., 1996).

Hyponatremia

By impairing the dilution of the tubular fluid, thiazides reduce the capacity for rapid and effective elimination of free water, and slight, asymptomatic falls in serum sodium concentration are common (Wilcox, 1999). Rarely, severe, symptomatic hyponatremia develops, usually soon after diuretics are started in elderly women who

appear to have an expanded fluid volume from increased water intake in the face of a decreased ability to excrete free water (Clark et al., 1994).

Erectile Dysfunction

Impotence may be more common with diuretics than with other drugs. In the large, randomized Medical Research Council (MRC) trial, impotence was reported by 22.6% of the men on bendrofluazide, as compared to a rate of 10.1% among those on placebo and 13.2% among those on propranolol [Medical Research Council Working Party (MRC), 1981]. In the Treatment of Mild Hypertension Study (TOMHS), the men randomized to chlorthalidone had a 17.1% incidence of erection problems through 24 months, as compared to an 8.1% incidence in those on placebo (Grimm et al., 1997).

Other Side Effects

Fever and chills, blood dyscrasias, cholecystitis, pancreatitis, necrotizing vasculitis, acute interstitial nephritis, and noncardiogenic pulmonary edema have been seen rarely. Excess volume depletion may induce prerenal azotemia and favor thrombosis (Lottermoser et al., 2000). Allergic skin rashes occur in 0.28% of patients, and approximately the same percentage develops photosensitivity (Diffey and Langtry, 1989). As will be noted, an increased relative risk of renal cell (and perhaps colon) cancer has been reported with diuretic therapy (Lip and Ferner, 1999), but the absolute risk is far below the proven benefits of these drugs.

Conclusion

Diuretics can cause multiple metabolic perturbations that could reduce their ability to protect against progressive atherosclerosis as they lower BP. Clearly, these adverse effects are dose dependent and much less of a problem with appropriately lower doses (6.25 mg HCTZ in combination, 12.5–25.0 mg HCTZ alone), doses that will provide most, if not all, of their antihypertensive effects. Larger doses may be needed, but low doses should always be tried and, when they work, should be maintained for as long as the patient is being treated. When withdrawn, the BP will usually promptly rise (Walma et al., 1997).

Loop Diuretics

Loop diuretics primarily block chloride reabsorption by inhibition of the $Na^+/K^+/Cl^-$ cotransport system of the luminal membrane of the thick ascending limb of Henle's loop, the site where 35% to 45% of filtered sodium is reabsorbed (Fig. 7-2). Therefore, the loop diuretics are more potent and have a more rapid onset of action than do the thiazides. However, they are no more effective in lowering BP or less likely to cause side effects if given in equipotent amounts. Their major use is in patients with renal insufficiency, in whom large enough doses can be given to achieve an effective luminal concentration (see Chapter 9). In addition, when given intravenously, they provide rapid vasodilative effects in addition to their diuretic action (Dormans et al., 1996).

Furosemide (Lasix)

Clinical Use

Although some report good antihypertensive effects from once-daily 40-mg doses of furosemide (van der Heijden et al., 1998), most find that even twice-daily furosemide is less effective than twice-daily HCTZ (Anderson et al., 1971; Araoye et al., 1978; Holland et al., 1979) or once-daily chlorthalidone (Healy et al., 1970) while producing similar hyperuricemia and hypokalemia. The maintenance of a slightly shrunken body fluid volume, which is critical for an antihypertensive action from diuretic therapy, is not met by the short duration of furosemide action (<6 hours for an oral dose); during the remaining hours sodium is retained, so that net fluid balance over 24 hours is left unaltered (Wilcox et al., 1983). If furosemide is used twice daily, the first dose should be given early in the morning and the second in the midafternoon, both to provide diuretic action at the time of sodium intake and to avoid nocturia.

One indication for the use of a loop diuretic is in patients on lithium who may have a rise in serum levels when given a thiazide, presumably from enhanced proximal reabsorption of lithium. With furosemide, no increase was seen, perhaps because lithium reabsorption in the loop of Henle was blocked (Jefferson and Kalin, 1979). The bioavailability of different furosemide products was found to vary from 12% to 112%, so caution is needed in switching brands (Murray et al., 1997).

Side Effects

Loop diuretics may cause fewer metabolic problems than do longer-acting agents, because of their shorter duration of action (Reyes and Taylor, 1999). With similar durations of action, the side effects are similar. Pancreatitis (Stenvinkel and Alvestrand, 1988) and allergic reactions (Sullivan, 1991) are two more of the thiazide-associated problems also seen with furosemide.

Bumetanide (Bumex)

Bumetanide, although 40 times more potent and 2 times more bioavailable than furosemide on a weight basis, is identical in its actions when given in an equivalent dose (Brater et al., 1983).

Torsemide (Demadex)

Torsemide differs from the other diuretics in that it is mainly eliminated by hepatic metabolism, with only 20% being excreted unchanged in the urine (Brater, 1993). Therefore, it has a more prolonged duration of action, as long as 12 hours.

In small doses of 2.5 to 5.0 mg, torsemide may lower BP in uncomplicated hypertension, whereas larger doses are needed for chronic edematous states or with renal insufficiency (Dunn et al., 1995). With small doses, minimal potassium wastage occurs.

Ethacrynic Acid (Edecrin)

Although structurally different from furosemide, ethacrynic acid also works primarily in the ascending limb of Henle's loop and has an equal potency. It is used much less than furosemide, mainly because of its greater propensity to cause permanent hearing loss. Its main use is in patients with sulfonamide sensitivity.

Potassium-Sparing Agents

Potassium-sparing agents act in the distal tubule to prevent potassium loss, one (spironolactone) as an aldosterone antagonist, the others (triamterene and amiloride) as direct inhibitors of potassium secretion (Saggar-Malik and Cappuc cio, 1993). All three are effective in reducing diuretic-induced K^+ wastage, but progressive hypokalemia may still occur with their use (Sawyer and Gabriel, 1988). Caution is needed with their use in the presence of renal insufficiency, wherein hyperkalemia may develop because of the decreased ability to excrete potassium.

Spironolactone (Aldactone)

Clinical Use

The similarities in the structure of spironolactone to that of the mineralocorticoid hormones enable this drug, when given in relatively large amounts, to inhibit competitively the binding of those steroids to their intracellular receptors, thereby antagonizing their physiologic effects. This antagonism has been used clinically in three ways:

- As a diagnostic test and relatively specific therapy for the hypertension associated with primary aldosteronism (see Chapter 13).
- As a diuretic in chronic edematous states, wherein high levels of aldosterone play a major role.
- As an inhibitor of the aldosterone-mediated exchange of Na^+ and K^+ in the distal tubule to prevent the potassium wastage from thiazide diuretics. When used in

combination with HCTZ (as in Aldactazide), 25 mg spironolactone provided an increase in plasma K^+ comparable to that of 32 mmol KCl (Toner et al., 1991).

Spironolactone will provide a significant anti-hypertensive effect on its own if given in modest doses. When used alone in average doses of 100 mg once per day, it produced a fall in BP of 18/ 10 mm Hg over a mean follow-up of 20 months (Jeunemaitre et al., 1988). The antihypertensive efficacy of spironolactone is greater in patients with lower plasma renin and higher aldosterone levels (Lim et al., 1999).

In keeping with the experimental evidence by Struthers (1999), Weber (Soberman and Weber, 2000), and their colleagues that spironolactone induces a number of beneficial effects, including an inhibition of myocardial and renal fibrosis, the Randomized Aldactone Evaluation Study found a 30% decrease in mortality in patients with severe heart failure who were given 25 mg of the drug on top of their other medications (Pitt et al., 1999). Whether such benefits will be seen under other conditions, including usual hypertension, remains to be seen. While awaiting even more specific aldosterone antagonists (e.g., eplerenone), which should be even easier to take, a low dose of spironolactone with a thiazide (Aldactazide) is a rational potassium-sparing agent that could turn out to be better than any other.

Side Effects

Impotence and gynecomastia in men and breast tenderness in women are the major side effects. With doses of 25 to 50 mg per day, gynecomastia was seen in 30 of 431 men (Jeunemaitre et al., 1988). The natriuresis induced by spironolactone is antagonized by aspirin (Tweeddale and Ogilvie, 1973).

Triamterene (Dyrenium)

Although triamterene has less intrinsic antihypertensive action than does spironolactone, it acts to inhibit potassium wasting with no hormonal side effects. It enhances the natriuretic effect of thiazides while minimizing their kaliuretic effect and preserves serum and muscle potassium and magnesium levels (Widmann et al., 1988).

Clinical Use

For many years, a combination of HCTZ (25 mg) and triamterene (50 mg), marketed as Dyazide, was the most widely prescribed antihypertensive drug in the United States. A more bioavailable tablet formulation of HCTZ and triamterene (Maxzide) has been marketed and shown to have equal antihypertensive efficacy (Casner and Dillon, 1990).

Side Effects

Triamterene may be excreted into the urine and may find its way into renal stones (Sörgel et al., 1985). However, no higher frequency of hospitalization for renal stones was found among users of triamterene than among users of HCTZ alone or in combination with other drugs (Jick et al., 1982). The simultaneous use of triamterene and the prostaglandin inhibitor indomethacin has been reported to induce reversible acute renal failure (Sica and Gehr, 1989). Because triamterene is a folic acid antagonist, it should not be used during pregnancy (Hernández-Díaz et al., 2000).

Amiloride (Midamor)

Amiloride, structurally different from both spironolactone and triamterene, inhibits a number of transport proteins that facilitate the movement of sodium ions either alone or linked with hydrogen or calcium. By blocking the entry of sodium into distal convoluted tubular cells, potassium loss through potassium channels is diminished (Rose, 1991).

Clinical Use

Amiloride has some antihypertensive effect of its own (Katzman et al., 1988) and may therefore potentiate the effect of thiazide diuretics while blunting the renal wastage of potassium and magnesium. It is largely used in combination with HCTZ as in Moduretic, which contains 50 mg HCTZ and 5 mg amiloride. Other uses than as a potassium sparer may be developed: By blocking Na^+-H^+ exchange, it inhibits the rise in intracellular calcium during myocardial ischemia (Murphy et al., 1991). In addition, its action in sodium channels involved in taste may diminish the stimulation of sodium intake that accompanies the use of diuretics (Mattes and Engelman, 1992). Moreover, amiloride blocks the access of lithium to the tubular cells, ameliorating the antidiuretic hormone–resistant polyuria often seen with chronic lithium therapy (Battle et al., 1985).

Side Effects

Nausea, flatulence, and skin rash have been the most frequent side effects and hyperkalemia the most serious. Moreover, a number of cases of hyponatremia in elderly patients have been reported after its use in combination with HCTZ (Mathew et al., 1990).

ADRENERGIC-INHIBITING DRUGS

Of the adrenergic-inhibiting agents currently used to treat hypertension, some act centrally on a $_2$-receptors to inhibit sympathetic nerve activity, some inhibit postganglionic sympathetic neurons, and some block the a- or badrenoreceptors on target organs (Fig. 7-6). Agents that act by blocking ganglia are no longer used.

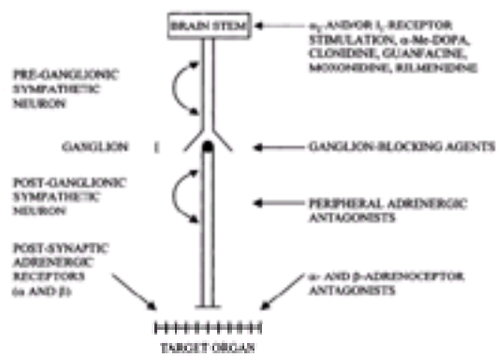


FIG. 7-6. Drug targets in the sympathetic nervous system. Virtually all structures, neurons, and receptors of the sympathetic nervous system can be influenced more or less selectively by antihypertensive drugs. a-Me-DOPA, a-Methyl-dioxyphenylalanine. (Modified from van Zwieten PA. Beneficial interactions between pharmacological, pathophysiological and hypertension research. *J Hypertens* 1999a;17: 1787–1797.)

Central a-Agonists

Central a agents stimulate central a_{2a}-adrenergic receptors that are involved in depressor sympathoinhibitory mechanisms (van Zwieten, 1999b) (Fig. 7-7). Some are selective, whereas clonidine also acts on central imidazoline receptors. These drugs have well-defined effects, including

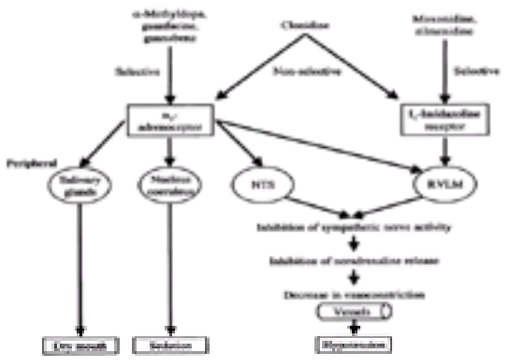


FIG. 7-7. Central antihypertensive mechanisms of various types of centrally acting antihypertensive drugs. Note the different targets of a $_2$-adrenoceptor agonists and I_1-imidazoline stimulants. The adverse reactions, dry mouth and sedation, are mediated by a $_2$-adrenoceptors but not by I_1-imidazoline receptors. NTS, nucleus tractus solitarii; RVLM, rostral ventrolateral medulla. [Modified from van Zwieten PA. The renaissance of centrally acting antihypertensive drugs. J Hypertens 1999b;17(Suppl 3):S15–S21.]

- A marked decline in sympathetic activity reflected in lower levels of norepinephrine.
- A reduction of the ability of the baroreceptor reflex to compensate for a decrease in BP, accounting for the relative bradycardia and enhanced hypotensive action noted on standing.
- A modest decrease in both peripheral resistance and cardiac output.
- A fall in plasma renin levels.
- Fluid retention, which may not occur with guanabenz.
- Maintenance of renal blood flow despite a fall in BP.
- Common side effects reflecting their central site of action: sedation, decreased alertness, and a dry mouth.

When central a-agonists are abruptly stopped, a rapid rebound and, rarely, an overshoot of the BP may be experienced with or without accompanying features of excess sympathetic nervous activity. This discontinuation syndrome likely represents a sudden surge of catecholamine release, freed from the prior state of inhibition.

Methyldopa (Aldomet)

From the early 1960s to the late 1970s, when b-blockers became available, methyldopa (Aldomet) was the second most popular drug (after diuretics) used to treat hypertension.

Pharmacology

Methyldopa is the a-methylated derivative of dopa, the natural precursor of dopamine and norepinephrine. Its mode of action involves the formation of methylnorepinephrine, which acts as a potent agonist at a-adrenergic receptors within the central nervous system (CNS) (van Zwieten, 1999b).

Efficacy and Dosage

BP is lowered maximally approximately 4 hours after an oral dose of methyldopa, and some effect persists for up to 24 hours. For most patients, therapy should be started with 250 mg two times per day, and the daily dosage can be increased to a maximum of 3.0 g on a twice-per-day schedule. In patients with renal insufficiency, the dosage should be halved.

Side Effects

In addition to the anticipated sedative effects, postural hypotension, and fluid retention, an impairment of reticuloendothelial function (Kelton, 1985) and a variety of autoimmune side effects, including fever and liver dysfunction, are peculiar to methyldopa. These may reflect an inhibition of suppressor T cells with resultant unregulated autoantibody production by B cells (Kirtland et al., 1980). Liver dysfunction usually disappears when the drug is stopped, but at least 83 cases of serious hepatotoxicity were reported by 1975 (Rodman et al., 1976), with diffuse parenchymal injury similar to autoimmune chronic active hepatitis (Lee, 1995).

An impairment of psychometric performance (Johnson et al., 1990) and a selective loss of upper airway motor activity (Lahive et al., 1988) may not be obvious until the drug is stopped. Overall, in large surveys, the number and range of the adverse reactions to methyldopa are impressive (Webster and Koch, 1996). In view of its unique and potentially serious side effects, I believe other central a-agonists should be used in place of methyldopa. In the United States, it remains a favored drug only for the treatment of hypertension during pregnancy (see Chapter 11).

Guanabenz (Wytensin)

Guanabenz, an aminoguanidine, works like clonidine and methyldopa and causes similar side effects; unlike these other agents, it offers the advantages of not causing reactive fluid retention, so it has been approved for initial use as monotherapy. Its use is usually associated with slight lowering of serum cholesterol (Kaplan and Grundy, 1988), and it can be safely used in diabetics (Gutin and Tuck, 1988) and asthmatics (Deitch et al., 1984).

Therapy should begin with 4 mg twice per day, with increments up to a total of 64 mg per day.

The side effects mimic those seen with other central a$_2$-agonists; sedation and dry mouth are the most prominent, being seen in 20% to 30% of patients. A withdrawal syndrome may occur if the drug is stopped abruptly (Ram et al., 1979).

Guanfacine (Tenex)

Another selective central a$_2$-agonist, guanfacine appears to enter the brain more slowly and to maintain its antihypertensive effect longer then guanabenz (Sorkin and Heel, 1986). These differences translate into a once-per-day dosage and perhaps fewer CNS side effects (Lewin et al., 1990). Withdrawal symptoms are less common than with clonidine (Wilson et al., 1986). These characteristics make it the most attractive of this group of centrally acting a $_2$-agonists.

Clonidine (Catapres)

Clonidine acts centrally on both a $_2$-receptors and imidazoline receptors (Fig. 7-7). It is readily absorbed, and plasma levels peak within an hour; the plasma half-life is 6 to 13 hours. When taken orally, the BP begins to fall within 30 minutes, with the greatest effect occurring between 2 and 4 hours. The duration of effect is from 12 to 24 hours.

Clinical Use

The starting dose may be as little as 0.075 mg twice daily (Clobass Study Group, 1990), with a maximum of 1.2 mg per day. Repeated hourly doses of 0.1 to 0.2 mg have been used to lower markedly elevated BP (Houston, 1986). Clonidine has been used to prevent the reflex sympathetic overactivity that follows direct vasodilator therapy (Mitchell and Pettinger, 1981) and to serve as a screening test for pheochromocytoma (see Chapter 12).

A transdermal preparation that delivers clonidine continuously over a 7-day interval has been found to be effective and to cause milder side effects than oral therapy

(Giugliano et al., 1998), but it may cause considerable skin irritation and side effects similar to those seen with the oral drug (Langley and Heel, 1988), including rebound hypertension when discontinued (Metz et al., 1987). It is available in doses of 0.1, 0.2, and 0.3 mg per day.

Side Effects

Clonidine and methyldopa share the two most common side effects, sedation and dry mouth, although these effects are more common with clonidine (Webster and Koch, 1996). Clonidine does not share the autoimmune hepatic and hematologic derangements induced by methyldopa. Depression of sinus and atrioventricular (AV) nodal function may be common, and a few cases of severe bradycardia have been reported (Byrd et al., 1988). Large overdoses will lead to hypertension, presumably by stimulation of peripheral a receptors, causing vasoconstriction (Hunyor et al., 1975).

Rebound and Discontinuation Syndromes

If any antihypertensive therapy is inadvertently stopped abruptly, various discontinuation syndromes may occur: (a) a rapid asymptomatic return of the BP to pretreatment levels, which occurs in the majority of patients; (b) a rebound of the BP plus symptoms and signs of sympathetic overactivity; and (c) an overshoot of the BP above pretreatment levels. In addition, patients who suddenly stop use of b-blockers may experience a different discontinuation syndrome manifested by the sudden appearance of coronary ischemia.

A discontinuation syndrome has been reported with most currently used drugs, but most frequently with clonidine (Neusy and Lowenstein, 1989), likely reflecting a rapid return of catecholamine secretion that had been suppressed during therapy.

Those who take high doses of any antihypertensive drug are vulnerable, particularly if they have underlying severe hypertension and high levels of renin-angiotensin. Those who had been on a combination of a central adrenergic inhibitor (e.g., clonidine) and a b-blocker may be particularly susceptible if the central inhibitor is withdrawn while the b-blocker is continued (Lilja et al., 1982). This leads to a sudden surge in plasma catecholamines in a situation in which peripheral a-receptors are left unopposed to induce vasoconstriction because the b-receptors are blocked and cannot mediate vasodilation.

If a discontinuation syndrome appears, the previously administered drug should be restarted, and the symptoms will likely recede rapidly. If needed, labetalol will effectively lower a markedly elevated BP (Mehta and Lopez, 1987).

Other Uses

Clonidine has been reported to be useful in numerous conditions that may accompany hypertension, including

- Restless legs syndrome (Wagner et al., 1996)
- Opiate withdrawal (Bond, 1986)
- Menopausal hot flashes (Pandya et al., 2000)
- Diarrhea due to diabetic neuropathy (Fedorak et al., 1985) or ulcerative colitis (Lechin et al., 1985)
- Sympathetic nervous hyperactivity in patients with alcoholic cirrhosis (Esler et al., 1992)
- Congestive heart failure (CHF) (Gavras et al., 1999)

Imidazoline Receptor Agonists

A new generation of centrally acting drugs is being promoted that has as its primary site of action the imidazoline receptor located in the rostral ventrolateral medulla oblongata, wherein a_2-receptors are less abundant (van Zwieten, 1999b). Two of these drugs, *rilmenidine* and *moxonidine*, are being used in Europe but have not been approved for use in the United States. They effectively reduce sympathetic activity (Greenwood et al., 2000) and may diminish insulin resistance (De Luca et al., 2000), with less of the sedation and dry mouth seen with clonidine and selective a $_2$-agonists (Fig. 7-7).

Peripheral Adrenergic Inhibitors

Reserpine

First reported to be an effective antihypertensive in the 1940s (Bhatia, 1942), reserpine became a popular drug in the 1960s and 1970s but has been used less and less for various reasons:

- Because it is an inexpensive generic drug, reserpine has no constituency pushing for its use (Fraser, 1996).
- Reserpine has become old hat; the advent of every new “miracle” antihypertensive makes it look more and more outdated.
- The scare of cancer tainted reserpine, although the claims have been refuted (Horwitz and Feinstein, 1985).
- Reserpine is associated with a lurking specter of insidious depression.

Pharmacology

Reserpine, one of the many alkaloids of the Indian snakeroot *Rauwolfia serpentine*, has all of the desirable pharmacologic actions of the plant's various preparations. Reserpine is absorbed readily from the gut, is taken up rapidly by lipid-containing tissue, and binds to sites involved with storage of biogenic amines. Its effects start slowly and persist, so only one dose per day is needed.

Mode of Action

Reserpine blocks the transport of norepinephrine into its storage granules so that less of the neurotransmitter is available when the adrenergic nerves are stimulated. The resultant decrease in sympathetic tone results in a decrease in peripheral vascular resistance. Catecholamines also are depleted in the brain, which may account for the sedative and depressant effects of the drug, and in the myocardium, which may decrease cardiac output and induce a slight bradycardia (Cohen et al., 1968).

Efficacy and Dosage

By itself, reserpine has limited antihypertensive potency, resulting in an average decrease of only 3/5 mm Hg; when combined with a thiazide, the reduction averaged 14/11 mm Hg (VA Cooperative Study, 1962). It works as well as other drugs (Krönig et al., 1997) and induces significant regression of LVH (Horn et al., 1997).

With a diuretic, as little as 0.05 mg once daily will provide most of the antihypertensive effect of 0.25 mg and is associated with less lethargy and impotence (Participating VA Medical Centers, 1982).

Side Effects

Side effects, which are relatively infrequent at appropriately low doses (Prisant et al., 1991), include

- Nasal stuffiness
- Increased gastric acid secretion, which rarely may activate an ulcer
- CNS depression, which may simply tranquilize an apprehensive patient and is rarely severe enough to lead to serious depression

Guanethidine (Ismelin)

Guanethidine at one time was frequently used for moderate hypertension because it requires only one dose per day and has a steep dose-response relationship, thus

producing an effect in almost every patient. As other effective drugs with fewer side effects became available, the use of guanethidine rapidly diminished.

Pharmacology

Guanethidine is taken into the adrenergic nerves by an active transport mechanism. Once inside the adrenergic nerves, guanethidine initially blocks the exit of norepinephrine; it then causes an active release of norepinephrine from its storage granules, depleting the reserve pool of the neurotransmitter and decreasing the amount released when the nerve is stimulated, thereby reducing peripheral resistance. The BP is reduced somewhat in the supine position but much more so when the patient is upright, because the normal vasoconstrictive response to posture is blunted (Goldberg and Raftery, 1976).

Guanethidine has a steep dose-response relationship so that the more drug given, the greater the effect. The amount required to lower standing BP to an acceptable and tolerable level varies from 25 to 300 mg daily. The drug need be given only once daily, and the full hypotensive action of a given dose may not become manifest for several days.

Side Effects

Most of the complications are in keeping with the known effects of guanethidine: postural hypotension, fluid retention, diarrhea, and failure of ejaculation. The appearance of minimal postural hypotension is an indication that the therapeutic end point has been reached.

Guanadrel Sulfate (Hylorel)

A close relative of guanethidine, guanadrel sulfate has almost all the attributes of that drug with a shorter onset and offset of action, which diminish the frequency of side effects and make it more tolerable (Owens and Dunn, 1988).

a-Adrenergic Receptor Blockers

Selective a_1-blockers have had a relatively small share of the overall market for antihypertensive drugs in the United States (Fig. 7-1). Until 1987, prazosin (Minipress) was the only selective a-blocker available, but terazosin (Hytrin) and doxazosin (Cardura) are now available. The availability of more of these drugs, the increasing awareness of their special ability to improve lipid levels (Hirano et al., 2001) and insulin sensitivity, and their unique ability to quickly relieve the symptoms of benign prostatic hypertrophy (Lepor et al., 1997) support their more wide-spread use. However, the premature termination of the doxazosin arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in early 2000 (ALLHAT Officers and Coordinators, 2000) because of an increased incidence of heart failure will likely slow the expected increase in the use of a-blockers for treatment of hypertension. As will be noted, this step may have been premature but, in retrospect, was not surprising. Despite the disappointment of the ALLHAT data, there are multiple justifications for the continued use of this class of drugs.

Beyond their effectiveness in lowering BP (Black et al., 2000), these justifications include the recognition that a-adrenergic mechanisms are involved in such varied processes as coronary vasoconstriction (Heusch et al., 2000), cardiac hypertrophy (Hunter and Chien, 1999), and expression of contractile proteins in prostatic smooth muscle cells (Lin et al., 2001).

Mode of Action

The nonselective a-blockers phenoxybenzamine and phentolamine are used almost exclusively in the medical management of pheochromocytoma, because they are only minimally effective in primary hypertension (see Chapter 12).

After the two major subtypes of a-receptors were identified, prazosin was recognized to act as a competitive antagonist of postsynaptic a_1-receptors (Frishman and Kotob, 1999), and a number of others share this action (Table 7-4). These agents block the activation of postsynaptic a_1-receptors by circulating or neurally released catecholamines, an activation that normally induces vasoconstriction (Fig. 7-8). This blockade dilates both resistance and capacitance ves sels. Peripheral resistance falls without major changes in cardiac output, in part because of a balance between a decrease in venous return (preload) and a slight degree of reflex sympathetic stimulation as a consequence of the vasodilation.

Drug	Duration of action (h)	Peak of action (h)	Therapeutic dose (mg)	Frequency of administration (times per day)
Prazosin	4–6	0.5	1–20	2–3
Terazosin	>18	1.0–1.7	1–20	1–2
Doxazosin	18–36	6	1–16	1
Tamsulosin	>24	–	0.4–0.8	1
Indoramin	>6	2	50–150	2 or 3
Urapidil	6–8	3–5	15–120	1 or 2
Ketanserin	>12	1–2	20–40	1 or 2

Modified from Cubeddu LX. New alpha₁-adrenergic receptor antagonists for the treatment of hypertension: role of vascular alpha receptors in the control of peripheral resistance. Am Heart J 1998;116:1139–1150.

TABLE 7-4. *Comparative characteristics of a_1-antagonists*

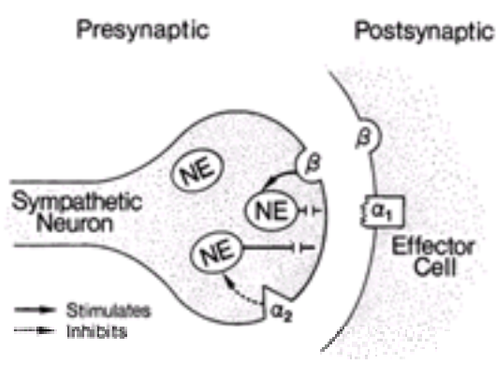


FIG. 7-8. Schematic view of the action of selective postsynaptic a_1-blockers. By blocking the a1-adrenergic receptor on the vascular smooth muscle, catecholamine-induced vasoconstriction is inhibited. The a_2-adrenergic receptor on the neuronal membrane is not blocked; therefore, inhibition of additional norepinephrine (NE) release by the short feedback mechanism is maintained.

The presynaptic a_2-receptors remain open, capable of binding neurotransmitter and thereby inhibiting the release of additional norepinephrine through a direct negative-feedback mechanism. This inhibition of norepinephrine release explains the lesser frequency of tachycardia, increased cardiac output, and rise in renin levels that characterize the response to drugs that block both the presynaptic a_2-receptor and the postsynaptic a_1-receptor (e.g., phentolamine). Despite this selective blockade, neurally mediated responses to stress and exercise are unaffected, and the baroreceptor reflex remains active. The decrease in preload and the blockade of a_1-receptors largely prevent the reflex sympathetic activation seen with direct vasodilators (e.g., hydralazine).

Accompanying these desirable attributes may be other actions that lessen the usefulness of aadrenergic blockers: They relax the venous bed as well and, at least initially, may affect the visceral vascular bed more than the peripheral vascular bed, and the subsequent pooling of blood in the viscera may explain the propensity to first-dose hypotension seen with the fast-acting prazosin (Saxena and Bolt, 1986). Volume retention is common (Bauer et al., 1984), perhaps because renin and aldosterone levels are less suppressed than they are with other adrenergic-inhibiting drugs (Webb et al., 1987).

Pharmacology

A quinazoline derivative, prazosin is rapidly absorbed, reaching maximal blood levels at 2 hours and having a plasma half-life of approximately 3 hours. Terazosin and doxazosin are less lipid-soluble and have half or less of the affinity for a $_1$-receptors as compared with prazosin. Therefore, they induce a slower and less profound initial fall in BP, particularly after standing, than does prazosin. This translates into a lesser propensity for hypotensive symptoms (Achari et al., 2000) and a longer duration of action for the second-generation a $_1$-blockers.

Tamsulosin produces a lesser blockade of the a $_1$-receptors on blood vessels than in the pros tate (Harada et al., 2000). It is not approved for treatment of hypertension.

Efficacy and Dosage

Multiple controlled studies have shown the anti-hypertensive efficacy of doxazosin and terazosin to be equivalent to that of diuretics, b-blockers, ACEIs, and CCBs (Achari et al., 2000; Levy et al., 1996; Neaton et al., 1993). The drugs work equally well in black and in nonblack patients (Batey et al., 1989) and in the elderly (Cheung et al., 1989) and can be effectively combined with a diuretic, b-blockers, or CCBs. In the presence of renal failure, the hypotensive action is enhanced, so lower doses should be used. The addition of doxazosin has been shown to control hypertension effectively in patients resistant to two or more other agents (Black et al., 2000).

The initial dose should be 1 mg, slowly titrated upward to achieve the desired fall in BP, with a total daily dose of up to 20 mg sometimes required. a-Blockers can be given at bedtime to provide a greater nocturnal fall in BP in patients who fail to have a normal dipping of BP during the night (Kario et al., 2000) and a maximal effect on the early morning surge in BP that is involved in the increased incidence of cardiovascular events at that time (Pickering et al., 1994). No tachyphylaxis to the antihypertensive action has been seen after 5 to 7 years of continual use of prazosin (Kincaid-Smith, 1987) or 3 years of doxazosin use (Talseth et al., 1991). However, if reactive fluid retention occurs, the BP may rise, only to fall again with the addition of a small dose of diuretic.

Side Effects

Side effects include headache, drowsiness, fatigue, and weakness—likely nonspecific effects of a lowering of the BP. Rather surprisingly, dizziness and asthma, the most common side effects seen in men given terazosin for benign prostatic hypertrophy, were not related to changes in BP (Lepor et al., 2000). For most patients, the side effects diminish with continued therapy. Rarely, a first-dose response of postural hypotension developing in 30 to 90 minutes is seen, particularly in volume-depleted patients given the shorter-acting prazosin (Stokes et al., 1977). The problem generally can be avoided by initiating therapy with a small dose and ensuring that the patient is not volume-depleted as a result of diuretic therapy. Urinary incontinence in women may be caused by a-blockers (Marshall and Beevers, 1996). Even massive overdoses do little harm if the patient remains supine (Lip and Ferner, 1995a).

Ancillary Effects

Exercise

During isotonic exercise, a $_1$-blockers do not reduce performance as may b-blockers but, on the other hand, they will not reduce the exercise-associated rise in systolic BP as well as b-blockers (Fahrenbach et al., 1995). During isometric exercise, an a $_1$-blocker will suppress the pressor response better than will a b-blocker (Hamada et al., 1987).

Cardiac Disease

Despite the theoretic advantages of a blockade on both coronary vasoconstriction and myocardial function and structure, these agents have not proved to be beneficial in either variant of angina (Winniford et al., 1983) or severe heart failure (Cohn et al., 1986). When added to metoprolol in patients in chronic CHF, doxazosin added no more lasting benefits to those seen with the b-blocker alone (Kukin et al., 1996).

LVH has been shown to regress after prazosin therapy (Agabiti-Rosei et al., 1992). This is not surprising, as a $_1$-receptor stimulation is the molecular mediator of cardiac myocyte hypertrophy.

Genitourinary Function

Doxazosin, tamsulosin, and terazosin have been found to provide excellent relief from the obstructive symptoms of benign prostatic hypertrophy (KL Cooper et al., 1999). In those who are also hypertensive, the expected fall in BP is noted; in those who are normotensive, little effect on BP is seen (Lepor et al., 1997). Beyond providing relief of obstructive symptoms (Rossi et al., 2001), doxazosin has been found to down-regulate expression of contractile proteins in prostate smooth muscle cells (Lin et al., 2001) and to induce apoptosis (Kyprianou et al., 1998), suggesting a possible reduction in the rate of growth of the gland.

In the TOMHS trial, which involved a representative from each of the five major classes of antihypertensives, only doxazosin reduced the incidence of impotence below that seen with placebo (Grimm et al., 1997).

Metabolic Effects

a $_1$-Blockers have been repeatedly found to improve both the lipid profile (Kasiske et al., 1995) and insulin sensitivity (Lithell, 1996). The mechanisms responsible for these generally favorable effects may include a decrease in fractional catabolic rate of HDL cholesterol (Sheu et al., 1990), an increase in lipoprotein lipase and lecithin-cholesterol acyltransferase activity (Rabkin, 1993), and an inhibition of LDL oxidation (Kinoshita et al., 2001). In addition, doxazosin has favorable effects on fibrinolysis (Jeng et al., 1996).

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Experience

Despite these generally attractive features, the termination of the doxazosin arm of the ALL-HAT (ALLHAT Officers, 2000) has been used as an argument to delete a-blockers from the list of first-line choices in the various guide-lines published in the late 1990s (Messerli, 2000). The ALLHAT data need to be carefully considered.

In the ALLHAT, more than 90% of the participants were on various antihypertensive drugs at the time of enrollment (Grimm et al., 2001). Their previous drugs were stopped abruptly or after one period of partial withdrawal, and they were started on their randomly allocated study drug (a-blocker, ACEI, CCB, or diuretic) as monotherapy. These enrollees were, overall, a high-risk population: significantly hypertensive, elderly, and with a high proportion of diabetics, dyslipidemics, blacks, and patients having had prior cardiovascular events. It is not, then, very surprising that some of these subjects switched from a diuretic with or without ACEI therapy to a low dose of an a-blocker would develop CHF as compared to those assigned to a diuretic.

At the same time, neither cardiovascular nor all-cause mortality was increased in the doxazosin group, suggesting that the twofold increased numbers of heart failure likely were not of severe degree. Moreover, the diagnosis of CHF was based on clinical grounds and was much more commonly observed in the ALL-HAT than in other randomized, controlled trials (RCTs) with equally severe hypertension (Brown, 2001).

The ALLHAT investigators went to considerable lengths to point out that the CHF rate in those on doxazosin was likely *not* increased beyond what has been seen

without therapy in multiple placebo-controlled trials, despite the worse cardiovascular risk status of the ALLHAT participants. They also noted that “the use of doxazosin as part of a multi-drug regimen for treating hypertension alone or hypertension with symptoms of benign prostatic hypertrophy was not tested in this trial” (ALLHAT officers, 2000).

I believe that the doxazosin arm of ALLHAT could have been continued in the absence of any increase in mortality. Nonetheless, the ALLHAT experience clearly indicates the need to use an a-blocker with a diuretic for the treatment of hypertension, particularly in those with LVH or other risk factors for CHF. a-Blockers remain useful as add-on therapy in patients with resistant hypertension (Black et al., 2000). They remain the preferred initial therapy for many patients with benign prostatic hypertrophy.

Other Agents

Urapidil

Urapidil has multiple sites of action, inducing vasodilation without tachycardia (van Zwieten, 1996).

Indoramin

Similar in structure and effect to prazosin, indoramin has been introduced for clinical use in numerous places outside the United States. It differs from prazosin in having a direct effect on the heart, reducing contractile force and rate, and it may cause more sedation and other central effects (Holmes and Sorkin, 1986).

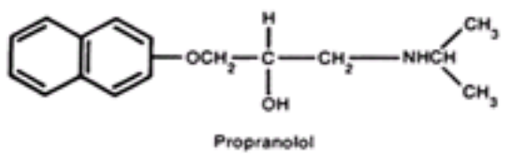
b-Adrenergic Receptor Blockers

For many years, b-adrenergic blocking agents were the second most popular antihypertensive drugs after diuretics (Fig. 7-1). Although they are no more effective than other antihypertensive agents and may, on occasion, induce serious side effects, they are generally well tolerated, and they offer the special advantage of relieving a number of concomitant diseases. In view of their proven ability to provide secondary cardioprotection after an acute MI, it was hoped that they would provide special primary protection against initial coronary events as well. As detailed in Chapter 5, this hope remains unfulfilled: When compared with a diuretic in middle-aged patients, no significant difference between the two drugs in protecting against coronary mortality was noted in two large trials (MRC, 1985; Wilhelmsen et al., 1987), although half of the patients in one trial who received the b-blocker metoprolol did have a lower coronary death rate than did those on a diuretic (Wikstrand et al., 1991). In the MRC trial in the elderly (MRC, 1992), the b-blocker was significantly less effective than was the diuretic in protecting against coronary disease, so that Messerli et al. (1998) advise against the use of b-blockers in the elderly.

Nonetheless, the proven benefits of b-blockers in patients with either coronary disease (particularly after an acute MI) or CHF ensure that these drugs will continue to be widely used.

Background

These agents are chemically similar to bagonists and to each other (Fig. 7-9). Propranolol was synthesized in 1963, described first in 1964 (Black et al., 1964), shown to be effective in treatment of hypertension that same year (Prichard and Gillam, 1964), and marketed in England in 1965.



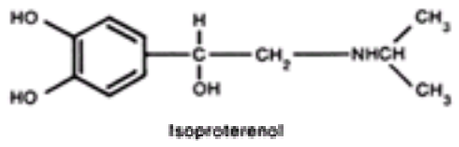


FIG. 7-9. Structure of propranolol and the b

Since then, a large series of similar drugs have been synthesized, approximately 20 being marketed throughout the world, 12 in the United States. They differ in a number of ways, some having clinical significance, others probably being irrelevant. The various b-blockers can be conveniently classified by their relative selectivity for the b_1-receptors (primarily in the heart) and presence of intrinsic sympathomimetic activity (ISA), also referred to as *partial agonist activity* (Fig. 7-10). In addition, some agents (labetalol, carvedilol) have both a- and b-blocking effects, and they are considered separately.

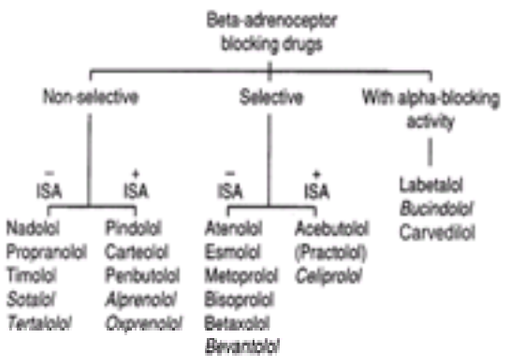


FIG. 7-10. Classification of b adrenoreceptor blockers based on cardioselectivity and intrinsic sympathomimetic activity. Drugs not approved for use in the United States for the treatment of hypertension are in italics. ISA, intrinsic sympathomimetic activity.

Mode of Action

The competitive inhibition of b-blockers on badrenergic activity produces numerous effects on functions that regulate the BP, including a reduction in cardiac output, a diminution of renin release, perhaps a decrease in central sympathetic nervous outflow, a presynaptic blockade that inhibits catecholamine release, and a probable decrease in peripheral vascular resistance.

The traditional view was that the primary effect is a reduction in cardiac output by 15% to 20%, resulting from the blockade of cardiac b_1-receptors, thereby reducing both heart rate and myocar dial contractility (Frohlich et al., 1968). However, the hemodynamic effects appear to change over time. This changing pattern was described by Man in't Veld et al. (1988) , who reviewed the literature on acute and chronic hemodynamic changes with b-blockers, covering 85 studies on ten drugs in a total of 912 patients, and observed a fairly uniform pattern: Cardiac output usually fell acutely (except with high-ISA pindolol) and remained lower chronically;

peripheral resistance, on the other hand, usually rose acutely but universally fell toward, if not to, normal with time.

Plasma Catechols

Despite the probable adaptation of peripheral resistance, plasma catecholamine levels are increased after b-blockade (Rosen et al., 1990); this reflects a reduction in the clearance of both epinephrine and norepinephrine from the circulation during b-blockade (Esler et al., 1981) as well as some baroreflex-mediated activation of the sympathetic nervous system.

Renin Release

Renin levels usually fall promptly after b-blocker therapy, reflecting a suppression of renin secretion by a reduction in the processing of prorenin and active renin (Blumenfeld et al., 1999).

Pharmacologic Differences

Three principal differences have an impact on the clinical use of b-blockers: lipid solubility, cardioselectivity, and ISA (Table 7-5). The first of these helps to determine the duration and constancy of action. The latter two help to determine the pattern of side effects. In clinical practice, these differences may not affect antihypertensive efficacy or the side effect profile in a major way (Fitzgerald, 1991), but they appear to translate into varying effects on mortality after MI: Those that are lipophilic, cardioselective, and without ISA have provided greater benefit than those with opposite properties (Soriano et al., 1997).

Drug	U.S. trade name	β_1-Selectivity	Intrinsic sympathomimetic activity	α-Blockage	Lipid solubility	Usual daily dosage (frequency)
Acebutolol	Sectral	+	+	–	+	200–1,200 mg (1)
Atenolol	Tenormin	++	–	–	–	25–100 mg (2)
Betaxolol	Kerlone	++	+	–	+	5–40 mg (1)
Bisoprolol	Zebeta	+++	–	–	+	2.5–20.0 mg (1)
Bucindolol	—	–	+	+	+	50–200 mg
Carteolol	Cartrol	–	+	–	–	2.5–10.0 mg (1)
Carvedilol	Coreg	–	–	+	+++	12.5–50.0 mg (2)
Celiprolol	Selectol	++	+	–	–	200–400 mg (1)
Esmolol	BreviBloc	++	–	–	–	25–300 μg/kg/min i.v.
Labetalol	Normodyne, Trandate	–	–	+	++	200–1,200 mg (2)
Metoprolol	Lopressor, Toprol-XL	++	–	–	++	50–200 mg (2, 1)
Nadolol	Corgard	–	–	–	–	20–240 mg (1)
Nebivolol	—	++	+	+	++	5–10 mg (1)
Penbutolol	Levatol	–	+	–	+++	10–20 mg (1)
Pindolol	Visken	+	+++	+	++	10–60 (2)
Propranolol	Inderal, LA	–	–	–	+++	40–240 mg (2, 1)
Timolol	Blocadren	–	–	–	++	10–40 mg (2)

+, ++, and +++ signs indicate the magnitude of the effect on various properties. – sign indicates no effect.

TABLE 7-5. *Pharmacologic properties of some b-blockers*

Lipid Solubility

b-Blockers have varying degrees of lipid solubility. Those that are more lipid-soluble (lipophilic) tend to be taken up and metabolized extensively by the liver. As an example, with oral propranolol and metoprolol, up to 70% is removed on the first pass of portal blood through the liver. The bioavailability of the b-blockers is, therefore, less after oral than after intravenous administration.

Those such as atenolol and nadolol, which are much less lipid-soluble (lipophobic), escape hepatic metabolism and are mainly excreted by the kidneys, unchanged. As a result, their plasma half-life and duration of action are much longer, and they achieve more stable plasma concentrations.

b_1-Receptor Cardioselectivity

All currently available b-blockers antagonize cardiac b_1-receptors competitively, but they vary in their degree of b_2-receptor blockade in extra-cardiac tissues. However, there seems to be little difference in antihypertensive efficacy among those that are more or less cardioselective (Fitzgerald, 1991). The major issue revolves around the protection from various side effects that might be anticipated from lesser degrees of b_2-receptor blockade in tissues such as bronchi, peripheral vessels, and pancreas.

The assumption that an agent with relative cardioselectivity is automatically less likely to cause side effects must be tempered by these considerations:

- No b-blocker is purely cardioselective, particularly in large doses.
- No tissue contains exclusively only one sub-group of receptors: The heart has both, with b_1 predominating; bronchioles have both, with b_2 predominating. Furthermore, the number of cardiac b_2-receptors increases after b_1-blockade (Hall et al., 1993).
- When high endogenous catechol levels are needed, as during an attack of asthma, even minimal degrees of b_2-blockade from a cardioselective drug such as bisoprolol may cause trouble (Haffner et al., 1992).
- Side effects may reflect not only a b_2-blockade of peripheral vasodilation but also b_1-mediated falls in cardiac output and limb blood flow.

Nonetheless, b_1-receptor cardioselective agents have some advantages. For instance, they have been shown to disturb lipid and carbohydrate metabolism less than do nonselective agents (Dujovne et al., 1993), and they will allow diabetics on insulin to raise their blood sugar level more rapidly in the event of a hypoglycemic reaction (Clausen-Sjöbom et al., 1987). Moreover, paradoxical pressor effects during major stresses are more likely to occur with nonselective b-blockers, probably because of their inhibition of peripheral b_2-mediated vasodilation, thereby allowing a-mediated vasoconstriction to go unopposed (Cleophas and Kauw, 1994).

On the other hand, in the presence of certain concomitant diseases, such as migraine and tremor, a nonselective b_2-antagonist effect may be preferable. Also, b_2-receptors are involved in stress-induced hypokalemia, so nonselective agents will block this fall in plasma potassium more than selective ones will (Brown et al., 1983). This could have clinical relevance, as stress-induced hypokalemia could cause sudden death. Nonetheless, b_1-selective agents have provided better reduction in risk than have non-selective agents in patients after an acute MI (Soriano et al., 1997).

Intrinsic Sympathomimetic Activity

Of the b-blockers now available in the United States, pindolol and, to a lesser degree, acebutolol have ISA, implying that even in concentrations that fully occupy the b-receptors, the biologic effect is less than that seen with a full agonist. When background sympathetic activity is low, the partial agonist acts as an agonist; when background activity is high, the partial agonist acts as an antagonist (Cruickshank, 1990).

The presence of ISA may be clinically reflected in various beneficial features: less bradycardia, less bronchospasm, less decrease in peripheral blood flow, and less derangement of blood lipids. However, Fitzgerald (1993) concludes “there is little convincing evidence from controlled clinical studies that partial agonism confers significant clinical benefit over full antagonists.”

Efficacy

In the usual doses prescribed (Table 7-5), various b-blockers have equal antihypertensive efficacy (Davidson et al., 1976; Wilcox, 1978). However, they may not all provide full 24-hour lowering of the BP, which may be particularly critical in protecting against early morning cardiovascular catastrophes. Metoprolol blunted this rapid early morning rise, but atenolol and pindolol did not (Raftery and Carrageta, 1985). Neutel et al. (1990) found a similar lack of 24-hour effect with once-daily atenolol

but a sustained effect with acebutolol.

Claims of lesser response to b-blockers also have been made for two groups of patients who tend to have lower renin levels: blacks and the elderly. The evidence showing a lesser response for blacks is persuasive and uniform (Saunders et al., 1990). However, the claim made by Bühler et al. (1982) that the elderly are less responsive seems to be invalid (Materson et al., 1993) but, in two large trials, b-blockers did not reduce coronary events in the elderly as well as did diuretics (Messerli et al., 1998).

Dosage

Most b-blockers have a flat dose-response curve, as has been demonstrated for propranolol (Serlin et al., 1980) and atenolol (Marshall et al., 1979). The combination with even a low dose of diuretic will enhance efficacy, as shown with 6.25 mg HCTZ and the b-blocker bisoprolol (Frishman et al., 1994).

Lipid-insoluble agents are removed mainly by renal excretion and have relatively longer serum half-lives. In patients with renal insufficiency, higher blood levels are seen with usual doses, so lower doses should be given (McAnish et al., 1980).

Choice of b-Blocker

In various clinical situations, preference may be given to b-blockers with certain characteristics (e.g., a noncardioselective agent for tremor or migraine). For the majority of patients with uncomplicated hypertension, considering all of these pharmacologic and clinical features, there seems to be some advantage in choosing a relatively cardioselective, lipid-insoluble agent to provide the certainty of prolonged action and the likelihood of fewer side effects.

Special Uses for b-Blockers in Hypertensives

b-Blockers have been proposed as initial monotherapy for most hypertensives, particularly those with coexisting conditions known to respond well to b-blockers, including coronary disease, heart failure, tremor, migraine, and stress-induced arrhythmias (Staessen et al., 1999).

Coexisting Coronary Disease

The antianginal and antiarrhythmic effects of b-blockers make them especially useful in hypertensive patients with coexisting coronary disease (Goldstein, 1996). Nonetheless, they have been given to fewer than 25% of patients known to have coronary heart disease (CHD) and no strong contraindications to their use (Wang and Stafford, 1998).

Even stronger evidence supports the routine use of b-blockers after an acute MI (Freemantle et al., 1999), including in patients with conditions often considered contraindications to b-blockade, such as diabetes, heart failure, and older age (Gottlieb et al., 1998). The greatest protection has been observed with noncardioselective, lipid-soluble, non-ISA agents, in particular propranolol, metoprolol, and timolol (Freemantle et al., 1999). In the elderly, lower doses of b-blocker may be as protective as higher doses and less likely to be associated with the development of heart failure (Rochon et al., 2000).

Congestive Heart Failure

Although b-blockers were formerly thought to be contraindicated in patients with heart failure, they have now been documented to be of value, first in those with idiopathic dilated cardiomyopathy but later in those with ischemic and other forms of systolic dysfunction (Abraham, 2000; Metra et al., 2000). As of now, excellent results have been reported with long-acting metoprolol, bisoprolol, and the a-b-blocker carvedilol (Abraham, 2000).

Hypertrophic Cardiomyopathy

b-Blockers are also useful in patients with hypertrophic cardiomyopathy, particularly for those with obstruction (Spirito et al., 1997).

Patients Needing Direct Vasodilator Therapy

When used alone, direct vasodilators set off reflex sympathetic stimulation of the heart. The simultaneous use of b-blockers prevents this undesired increase in cardiac output, which not only bothers the patient but also dampens the antihypertensive effect of the vasodilator.

Hyperkinetic Hypertension

Some hypertensive patients have increased cardiac output that may persist for many years. b-Blockers should be particularly effective in such patients, but a reduction in exercise capacity may restrict their use in young athletes.

Marked Anxiety and Stress

The somatic manifestations of anxiety—tremor, sweating, and tachycardia—can be reduced with b-blockers, which has been found useful for violin players, surgeons, race car drivers, and sufferers from phobias and panic attacks (Fogari et al., 1992). Atenolol protected patients with acute head injury from stress-induced cardiac damage (Cruickshank et al., 1987) and patients with coronary disease during surgery (Mangano et al., 1996). Propanolol given to patients with severe burns reversed muscle-protein catabolism (Herndon et al., 2001).

Side Effects

The side effects of b-blockers reflect the blockade of both b_1- and b_2-receptors. The more cardioselective b-blockers would be expected to induce fewer b_2 effects, and this has been noted (Fodor et al., 1987).

Central Nervous System

CNS side effects—insomnia, nightmares, depressed mood—occur in some patients, although probably less frequently with b_1-selective agents. However, in a randomized, placebo-controlled trial with propranolol, 80 to 400 mg per day, Pérez-Stable et al. (2000) found no greater incidences of depression, sexual dysfunction, or cognitive loss in those who received the nonselective b-blocker.

Carbohydrate Metabolism

Diabetics may have additional problems with b-blockers. The responses to hypoglycemia—both the symptoms and the counterregulatory hormonal changes that raise the blood sugar level— are largely mediated by epinephrine, particularly in those who are insulin-dependent because they usually are also deficient in glucagon. If these patients became hypoglycemic, the b-blockade of epinephrine responses delays the return of the blood sugar. The only symptom of hypoglycemia may be sweating, which may be enhanced in the presence of a b-blocker (Molnar et al., 1974). The more cardioselective b-blockers are preferable for those susceptible to hypoglycemia (Clausen-Sjöbom et al., 1987), but all b-blockers may delay recovery.

The larger population of nondiabetic hypertensives may be at a higher risk for developing diabetes when treated with b-blockers (Gress et al., 2000). The effect may reflect increased insulin resistance, as shown with multiple b-blockers (Jacob et al., 1998). In addition, weight gain may be more common with b-blockers than with other drugs (Sharma et al., 2001). Nonetheless, if a diabetic has a clear indication for a b-blocker, as after an acute MI, he or she should not be deprived the benefit.

Lipid Metabolism

b-Blockers without ISA raise serum triglycerides and lower the HDL cholesterol level, with little effect on total and LDL cholesterol levels (Kasiske et al., 1995). The effects are lessened with cardioselective agents and generally are not seen with agents having ISA (e.g., pindolol) or vasodilative effects (e.g., celiprolol) (Fogari et al., 1999b).

Pulmonary Function

Even topical timolol used for treatment of glaucoma may induce bronchospasm (Diggory et al., 1995). With a cardioselective agent, fewer users will get into trouble; and, if they do, they can respond better to an inhaled b-agonist.

Renal Function

Although chronic use of propranolol was shown to reduce glomerular filtration rate (GFR) and renal blood flow, no such falls in renal function were noted in patients given atenolol or nadolol (Bauer, 1985).

Potassium Levels

A slight rise in serum potassium may be seen with chronic use of b-blockers (Traub et al., 1980). These effects likely reflect blockade of the b_2-mediated epinephrine activation of the Na^+/K^+-ATPase pump that normally transports potassium from extracellular fluid into cells (Rosa et al., 1980).

Calcium Metabolism

After 6 months on various b-blockers, patients experienced an increase in plasma ionized calcium and phosphate levels and a decrease in urinary calcium excretion (Lind et al., 1994). This pattern was attributed to reduced calcium binding to albumin, increasing ionized calcium, which suppresses parathyroid hormone. Whatever the mechanism, b-blockers will correct the calcium leak that is often seen in hypertension.

Exercise Capacity

b-Blockers may reduce the ability to perform exercise and achieve cardiovascular fitness (Gordon et al., 1997), in part because of the more rapid onset of the feeling of fatigue and the subjective perception that exercise is harder to perform, which may arise more from central than from peripheral mechanisms (Cooper et al., 1988). Nonetheless, conditioning can be attained (Chick et al., 1988), probably more easily with cardioselective agents (Ronnevik et al., 1995).

Impotence

Impotence has been noted with b-blockers as with all antihypertensive agents. In the MRC trial, the frequency of impotence elicited by a questionnaire increased from 10.1% among those on placebo to 13.2% for those on propranolol (MRC, 1981).

Peripheral Circulation

Despite reports of vasospastic symptoms in the hand (Eliasson et al., 1984), an analysis of all 11 RCTs of b-blockers in patients with peripheral vascular disease found no evidence of worsening of intermittent claudication (Radack and Deck, 1991). Nocturnal muscle cramps have been reported with ISA b-blockers (Imai et al., 1995).

Skin and Connective Tissue

Practolol, the only b-blocker to possess an acetanilid structure, is the only one to cause a serious and progressive oculomucocutaneous syndrome (Wright, 1975).

Despite isolated case reports, there appears to be no causal connection between b-blockers and retroperitoneal fibrosis (Pryor et al., 1983). Psoriasis has been worsened by b-blockers (Savola et al., 1987).

Discontinuation Syndromes

In hypertensives taking b-adrenergic blockers, abrupt cessation may lead to withdrawal symptoms suggestive of sympathetic overactivity (Houston and Hodge, 1988). However, the more frequent and serious discontinuation syndrome is seen in patients with underlying coronary artery disease who may experience angina, infarction, or sudden death (Psaty et al., 1990). These ischemic episodes likely reflect the phenomenon of supersensitivity: An increased number of b-receptors appear in response to the functional blockade of receptors by the b-blocker; when the b-blocker is discontinued and no longer occupies the receptors, the increased number of receptors are suddenly exposed to endogenous catecholamines, resulting in a greater b-agonist response for a given level of catechols. Hypertensives, with a high frequency of underlying coronary atherosclerosis, may be particularly susceptible to this type of withdrawal syndrome; thus, when the drugs are discontinued, their dosage should be cut by half every 2 or 3 days, and the drugs should be stopped after the third reduction.

Overdose

Massive intoxication of b-blockers may cause profound hypotension, seizures, and coma, which are usually responsive to appropriate bagonist therapy (Halloran and Phillips, 1981).

a- and b-Adrenergic Receptor Blockers

Modification of the conventional b-blocker structure has provided agents with combined a- and b-blocking properties. Labetalol and carvedilol are now available.

Mode of Action

Both drugs block a_1-adrenoreceptors and badrenoreceptors. The ratio of a_1- to b-blockade for labetalol is 1:4 and for carvedilol is 1:10. The a_1-blockade provides those agents with vasodilative effects, unlike most other b-blockers. Pindolol is vasodilative because of its high level of ISA, whereas bucindolol has direct vasodilative effects independent of either ISA or a_1-blockade. Carvedilol in high concentrations also blocks calcium entry, and it has antioxidant effects (Frishman, 1998).

The hemodynamic consequences of the combined a- and b-blockade are a fall in BP, mainly via a fall in systemic vascular resistance, with little effect on cardiac output (Weber et al., 1998). The lack of reflex tachycardia is a consequence of b-blockade.

With labetalol, plasma renin activity decreases acutely and then rises, whereas norepinephrine levels increase (Weidmann et al., 1978). Weidmann et al. (1978) reported increased urinary excretion of catecholamines, but this has subsequently been found to be a chemical interference and not a true increase in excretion. As a result, diagnostic confusion may arise if workup for pheochromocytoma is done while the patient is on labetalol (see Chapter 12).

Efficacy and Dosage

Both labetalol and carvedilol are effective antihypertensives when given twice daily, maintaining good 24-hour control and blunting the early morning surges in pressure (Ruilope, 1994). The usual starting doses are 100 mg for labetalol and 6.25 mg for carvedilol; the maximal daily doses are 1,200 mg for labetalol and 50 mg for carvedilol.

Special Indications

Labetalol has been used both orally and intravenously to treat hypertensive emergencies, including postoperative hypertension (Lebel et al., 1985) and acute aortic dissection (Grubb et al., 1987). It has been successfully used to treat hypertension during pregnancy (Pickles et al., 1992).

Carvedilol has been shown to reduce the risk of death as well as the risk of hospitalization for cardiovascular causes in double-blind, placebo-controlled trials involving almost 1,500 patients with varying degrees of heart failure (Australia/ New Zealand Heart Failure Research Collaborative Group, 1997 ; Packer et al., 1996a). The dosage must be individualized and monitored closely (Frishman, 1998).

Side Effects

With both labetalol and carvedilol, symptomatic orthostatic hypotension is the most common side effect, seen most often during initial therapy with larger doses. A variety of other side effects have been seen with labetalol, including intense scalp itching, ejaculatory failure (Goa et al., 1989), and bronchospasm (George et al., 1985). An increased titer of antinuclear and antimitochondrial antibodies develops in some patients; although a systemic lupus syndrome has not been reported, lichenoid skin eruptions have been (Goa et al., 1989).

Perhaps the most serious side effect of labetalol is hepatotoxicity: At least three deaths have been reported (Clark et al., 1990). As a result, a warning has been added to its label in the United States, stating, “Hepatic injury may be slowly progressive despite minimal symptomatology. Appropriate laboratory testing should be done at the first symptom or sign of liver dysfunction” (*Physicians' Desk Reference*, 2000). Liver injury is less commonly seen with carvedilol (Frishman, 1998).

In keeping with its a-blocking effect, neither labetalol (Lardinois and Neuman, 1988) nor carvedilol (Lithell and Andersson, 1997) has as much of an adverse effect on lipids as do b-blockers.

DIRECT VASODILATORS

Drugs that enter the vascular smooth muscle cell to cause vasodilation are termed *direct* vasodilators. This is in contrast to those that vasodilate in other ways—by inhibiting hormonal vasoconstrictor mechanisms (e.g., ACEIs), by preventing calcium entry into the cells that initiate constriction (e.g., CCBs), or by blocking a-receptormediated vasoconstriction (e.g., a_1-blockers). The various vasodilators differ considerably in their power, mode of action, and relative activities on arteries and veins (Table 7-6).

Drug	Relative action on arteries (A) or veins (V)
Direct	
Hydralazine	A >> V
Minoxidil	A >> V
Nitroprusside	A + V
Diazoxide	A > V
Nitroglycerin	V > A
Calcium channel blockers	A >> V
Angiotensin-converting enzyme inhibitors	A > V
α-Blockers	A + V

>, greater than; >>, much greater than; +, equal on both.

TABLE 7-6. *Vasodilator drugs used to treat hypertension*

Hydralazine (Apresoline)

Hydralazine was introduced in the early 1950s (Freis et al., 1953) but was little used because of its activation of the sympathetic nervous system. Its use increased in the 1970s when the rationale for triple therapy—a diuretic, an adrenergic inhibitor, and a direct vasodilator—was demonstrated (Zacest et al., 1972). However, its use receded again with the advent of the newer vasodilating drugs that simultaneously block sympathetic activity. Today, despite its apparent ability to lower lipid levels (Perry and Schroeder, 1955) and to unload the left ventricle (Chatterjee et al., 1980), it is used, as is minoxidil, relatively infrequently, almost always as the third agent in treatment of severe hypertension.

Pharmacology

One of several phthalazine derivatives with hypotensive action, hydralazine has a short half-life but can persist for up to 24 hours. In patients with impaired renal function, the plasma half-life is greatly prolonged (Talseth, 1976).

The inactivation of hydralazine involves acetylation in the liver by the enzyme *N*-acetyltransferase. The level of this enzyme activity is genetically determined, and rapid acetylators require larger doses than do slow acetylators to achieve an equivalent effect (Ramsay et al., 1984). Perry (1973) showed that patients who develop a lupuslike toxicity tend to be slow acetylators and thus are exposed to the drug longer.

Mode of Action

In a manner that remains uncertain (Vidrio, 1990), hydralazine acts directly to relax the smooth muscle in the walls of peripheral arterioles, the resistance vessels more so than the capacitance vessels, thereby decreasing peripheral resistance and BP (Saxena and Bolt, 1986).

Coincidental to the peripheral vasodilation, the heart rate, stroke volume, and cardiac output rise, reflecting a baroreceptor-mediated reflex increase in sympathetic discharge (Lin et al., 1983) and direct stimulation of the heart (Khatri et al., 1977). In addition, the sympathetic over-activity and the fall in BP increase renin release (Eggertsen and Hansson, 1985), further counter-acting the vasodilator's effect and likely adding to the reactive sodium retention that accompanies the fall in BP (Fig. 7-11).

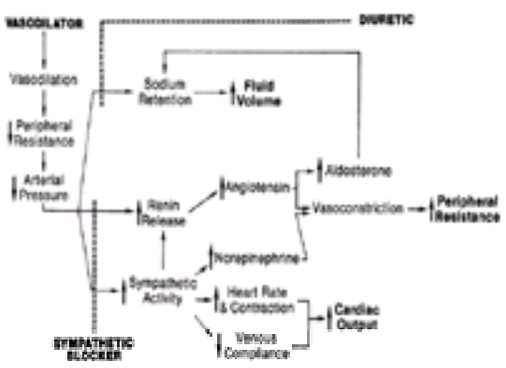


FIG. 7-11. Primary and secondary effects of vasodilator therapy in essential hypertension and the manner by which diuretic and b-adrenergic blocker therapy can overcome the undesirable secondary effects. (Modified from Koch-Weser J. Vasodilator drugs in the treatment of hypertension. Arch Intern Med

1974;133:1017–1027.)

These compensatory responses sharply limit the use of hydralazine by itself. Therefore, it has usually been given along with a b-blocker and a diuretic in the treatment of more severe hypertension (Fig. 7-11). NSAIDs attenuate its hypotensive action (Cinquegrani and Liang, 1986).

Dosage

Alone or in combination, hydralazine should usually be started at 25 mg two times per day. The maximal dose should probably be limited to 200 mg per day to lessen the likelihood of a lupuslike syndrome and because higher doses seldom provide additional benefit.

Side Effects

Three kinds of side effects are seen: those due to reflex sympathetic activation, those due to a lupuslike reaction, and those due to nonspecific problems. Headaches, flushing, and tachycardia should be anticipated and prevented by concomitant use of adrenergic inhibitors. The drug should be given with caution to patients with coronary artery disease and should be avoided in patients with a dissecting aortic aneurysm or recent cerebral hemorrhage, in view of its propensity to increase cardiac output and cerebral blood flow (CBF) (Schroeder and Sillesen, 1987).

Lupuslike Reaction

The lupuslike reaction has been described by Perry (1973), who reviewed his experience with 371 patients given the drug for as long as 20 years. An early, febrile reaction resembling serum sickness was seen in 11 patients; late toxicity developed in 44 (with serious symptoms in 14), resembling systemic lupus erythematosus or rheumatoid arthritis. These symptoms almost invariably went away when therapy was stopped or the dosage was lowered.

The lupuslike syndrome is clearly dose-dependent. In a prospective study of 281 patients, the syndrome did not occur in those taking 50 mg daily, whereas it occurred in 5.4% taking 100 mg daily and in 10.4% taking 200 mg daily (Cameron and Ramsay, 1984). The incidence was fourfold higher in women than in men, and 19.4% of women taking 200 mg daily developed the syndrome. A positive antinuclear antibody titer of 1:20 or higher occurs in 50% of patients taking hydralazine, of whom only 3% developed the lupus syndrome (Mansilla-Tinoco et al., 1982).

In addition to the lupuslike syndrome, a smaller number of patients develop a vasculitis primarily affecting the skin or kidneys (Short and Lockwood, 1995).

Other Side Effects

Other side effects of hydralazine include anorexia, nausea, vomiting, and diarrhea; less common effects are paresthesias, tremor, and muscle cramps. An additional potential disadvantage of hydralazine and other direct vasodilators is their failure when given alone to regress LVH, presumably because of their marked stimulation of sympathetic nervous activity (Leenen et al., 1987).

Minoxidil (Loniten)

More potent than hydralazine, minoxidil has become a mainstay in the therapy of severe hypertension associated with renal insufficiency (see Chapter 9). Its propensity to grow hair precludes its use in many women, but this effect has led to its use as a topical ointment for male-pattern baldness.

Pharmacology

A piperidinopyrimidine derivative, minoxidil has a plasma half-life of only 4 hours, but its antihypertensive effects persist for approximately 24 hours, and it can be used once daily (Johnson et al., 1986).

Mode of Action

Minoxidil induces smooth muscle relaxation by opening cardiovascular ATP-sensitive potassium channels, a mechanism apparently unique among vasodilators currently available in the United States but similar to the mode of action of various potassium channel openers (e.g., pinacidil) available elsewhere (Nielsen-Kudsk et al., 1996).

Because minoxidil is both more potent and longer lasting than hydralazine, it is not surprising that it turns on the various reactions to direct arteriolar vasodilation to an even greater degree. Therefore, large doses of potent loop diuretics and adrenergic blockers will be needed in most patients (see Fig. 7-11).

When used with diuretics and adrenergic inhibitors, minoxidil controls hypertension in more than 75% of patients whose disease was previously resistant to multiple drugs (MacKay et al., 1981). It can be given once daily in a range of 2.5 to 80 mg.

Side Effects

The most common side effect, seen in nearly 80% of patients, is hirsutism, beginning with fairly fine hair on the face and then with coarse hair increasing everywhere, including the external ear canal to the extent of causing hearing loss (Toriumi et al., 1988). It is apparently related to the vasodilation of the drug and not to hormonal effects. The hair gradually disappears when the drug is stopped, sometimes leaving less than before the drug was started (Kidwai and George, 1992). Beyond generalized volume expansion, pericardial effusions appear in approximately 3% of patients who receive minoxidil (Martin et al., 1980). Despite good control of hypertension with triple therapy including minoxidil, left ventricular size often continues to enlarge (Chrysant et al., 1991), but this can be prevented by addition of an ACEI (Pogátsu-Murray et al., 1997).

Other Direct Vasodilators

A number of other potassium channel openers are available elsewhere. Of these, pinacidil has been most extensively used (Ligtenberg et al., 1996). Other direct vasodilators that have been studied include flosequinan (Janssen et al., 1995), endralazine (Wu et al., 1986), and cadralazine (McTavish et al., 1990).

Nitrates, both nitroglycerin (Kawakami et al., 1995) and oral isosorbide (Stokes et al., 1999), by their vasodilating properties akin to endothelium-derived relaxing factor, can also be used as antihypertensives. Stokes et al. (1999) found isosorbide mononitrate to lower systolic BP to a greater degree than diastolic BP in ten elderly patients with resistant systolic hypertension. Hopefully, additional drugs that act selectively on large arteries to reduce pulse pressure will be developed (van Bortel et al., 1999 ; Wang et al., 2000). Intravenous direct vasodilators, in particular diazoxide and nitroprusside, are considered in the next chapter.

CALCIUM CHANNEL BLOCKERS

CCBs, called *calcium antagonists* by their leading advocate and developer, Fleckenstein (1990), were introduced as antianginal agents in the 1970s and as antihypertensives in the 1980s. They have rapidly grown to become the second most popular group of drugs used by U.S. practitioners for the treatment of hypertension in the early 2000s (Fig. 7-1).

Pharmacology

Three types of CCBs are now available. Another, mibefradil, was marketed but withdrawn. Those now available interact with the same calcium channel: the L-type

voltage-gated plasma membrane channel. They have major differences in their structure and cardiovascular effects (Angus et al., 2000) (Table 7-7).

System	Nifedipine	Diltiazem	Verapamil
Coronary vessels			
Tone	– – –	– –	– –
Flow	+++	++	++
Peripheral vasodilation	+++	+	++
Heart rate	++	–	–
Contractility	0, +	0, –	0, –
Atrioventricular node conduction	0	–	–

+ and – signs indicate the degree of effect on various systems; 0, no effect.
Modified from Triggle DJ. Pharmacologic and therapeutic differences among calcium channel antagonists. *Am J Cardiol* 1996;78(Suppl 9A):7–12.

TABLE 7-7. *Cardiovascular profile of calcium channel blockers*

Diltiazem, a benzothiazepine, and *verapamil*, a phenylalkylamine, are rate slowing: At equivalent concentrations, they induce vasodilation, depress cardiac contractility, and inhibit AV conduction.

Dihydropyridines are predominantly vasodilators. The first generation, exemplified by nifedipine, had modest effects on cardiac contractility. The second generation, such as amlodipine, felodipine, and nicardipine, has more effect on vascular dilation than on myocardial contractility or cardiac conduction. A number of other dihydropyridines are not yet approved in the United States but are being used elsewhere; these include benidipine, lacidipine, manidipine, and nitrendipine (Lüsher and Cosentino, 1998).

As described by Triggle (1996), various factors influence the actions of CCBs:

- Pharmacokinetics (e.g., nimodipine, which is distributed more into the CNS, affording a regional accumulation that has made it the agent of choice for relief of spasm around a subarachnoid hemorrhage).
- Mode of calcium mobilization affected.
- Class and subclass of calcium channel affected, with different subclasses of the L-type channel in different tissues.
- State-dependent interactions and pathologic state of tissue. The increased vascular tone of hypertension increases the binding of CCBs.

The vasodilative effects of CCBs may reflect more than their blockade of L-type calcium channels. CCBs increase endothelium-dependent vasodilation by restoring nitric oxide availability (Taddei et al., 2001), likely by an antioxidant effect on endothelial cells (Brovkovych et al., 2001). *In vitro*, they activate the interleukin-6 gene (Eickelberg et al., 1999) and inhibit carbonic anhydrase I activity (Puscas et al., 2000). *In vivo*, short-acting dihydropyridine CCBs acutely cause a reflex tachycardia associated with a reduced baroreceptor sensitivity; no such effect was seen with chronic therapy wherein baroreceptor sensitivity was increased (Vaile et al., 2000). As compared to verapamil, long-acting nifedipine was associated with less suppression of plasma norepinephrine and neither drug affected epinephrine or renin activity (Diamond et al., 2001).

Duration of Action

One of the major differences between older and newer CCBs is their duration of action. As shown in Table 7-8, some of these, such as the formulation of verapamil that affords 24-hour effectiveness, are provided by special delivery systems; others, such as amlodipine, have intrinsically long durations of action. The slow onset and long duration of action of amlodipine provide continued effects even if daily doses are missed (Leenen et al., 1996) and are associated with better long-term adherence to therapy (Sheehy and LeLorier, 2000).

Drug	Form and dose	Time to peak effect (h)	Elimination half-life (h)
Amlodipine	Tablet; 2.5–10.0 mg	6–12	30–50
Diltiazem[a]	Immediate-release tablet; dose varies	0.5–1.5	2–5
	Sustained-release tablet; 180–480 mg	6–11	2–5
Felodipine	Sustained-release tablet; 2.5–10.0 mg	2.5–5.0	11–16
Isradipine	Tablet; 2.5–10.0 mg	1.5	8–12
Nicardipine[a]	Immediate-release tablet; 20–40 mg	0.5–2.0	8
	Sustained-release tablet; 60–120 mg	?	8
Nifedipine	Immediate-release capsule; dose varies	0.5	2
	Sustained-release tablet; 30–120 mg	6	7
Nisoldipine	Sustained-release tablet; 20–40 mg	6–12	7–12
Verapamil[a]	Immediate-release tablet; dose varies	0.5–1.0	4.5–12.0
	Sustained-release tablet; 120–480 mg	4–6	4.5–12.0

[a]Also available in an intravenous formation, with a time to peak effect ranging from 5 to 15 minutes after administration.

TABLE 7-8. *Calcium channel blockers approved for use in the treatment of hypertension in the United States*

As has become increasingly obvious in the recent past, short-acting agents may induce abrupt falls in BP, which activate sympathetic nervous activity and thereby may incite coronary ischemia. Such effects are not seen with long-acting agents, which lower the BP gradually and smoothly (Hamada et al., 1998).

Efficacy

The currently available CCBs seem comparable in their antihypertensive potency, although no direct comparisons have been made among all of them. They have been used alone, in combination with other agents, and in the treatment of refractory hypertension and hypertensive crisis. In patients whose disease was inadequately controlled on two drugs (i.e., a diuretic and an ACEI), the addition of a CCB (nifedipine) usually provided satisfactory control (Cummings et al., 1991). Moreover, additive antihypertensive efficacy has been found when a dihydropyridine CCB is combined with either diltiazem or verapamil (Saseen et al., 1996).

Determinants of Efficacy

Age

What some have noted as an apparently greater antihypertensive effectiveness of CCBs in the elderly (Lacourcière et al., 1995) may reflect the characteristically higher systolic BP levels of the elderly and the more pronounced efficacy of CCBs as the level of BP increases (Donnelley et al., 1988). Elderly patients may be more responsive because of pharmacokinetic changes that increase the bioavailability of various CCBs, providing more active drug at any given dose than in younger patients (Lernfelt et al., 1998).

Race

Most comparisons have shown that blacks respond to CCBs as well as or better than do nonblacks. They respond better to CCBs than to ACEIs or to b-blockers (Materson et al., 1993; Saunders et al., 1990) and, in an open-label trial from South Africa, respond better to a CCB than to diuretics (Sareli et al., 2001).

Additive Effect of Diuretic or Low Sodium Intake

Long-acting nifedipine gastrointestinal therapeutic systems increased PRA levels but did not raise the plasma aldosterone levels commensurately (Fiad et al., 1997). This relative inhibition of aldosterone may play some role in the initial natriuretic and eventual antihypertensive effect of the drug. Moreover, a decrease in the antihypertensive efficacy of these drugs has been claimed under two conditions wherein renin levels are raised: dietary sodium restriction (Valdés et al., 1982) and concomitant diuretic therapy (Magagna et al., 1986).

Numerous studies have examined these relationships. In general, the findings support the view that dietary sodium restriction may reduce (but not abolish) the antihypertensive effect of CCBs, whereas high sodium intake may enhance (or not diminish) their efficacy (Luft et al., 1991; Nicholson et al., 1987). The explanation may be simple: CCBs have a mild natriuretic effect (Krekels et al., 1997); this effect would be more obvious in the presence of a higher sodium diet so that the BP would fall more. With a low sodium intake, this natriuretic effect would not be as pronounced, so the BP would diminish less. This explanation fits with the observation that the fall in BP with a CCB is greater in more sodium-sensitive patients (Damasceno et al., 1999).

On the other hand, most well-controlled studies have shown an additional antihypertensive effect when diuretics are combined with CCBs (Stergiou et al., 1997). The combination of a diuretic with a CCB has been shown to provide additive effects equal to those seen when a diuretic is added to a b-blocker (Thulin et al., 1991) or to an ACEI (Elliott et al., 1990).

Potential for Good or Bad Renal Effects

The increased excretion of sodium and water likely reflects the unique ability of CCBs, unlike other vasodilators, to maintain or increase effective renal blood flow, GFR, and renal vascular resistance, which, in turn, has been attributed to their selective vasodilative action on the renal afferent arterioles (Zanchi et al., 1995). On the surface, this preferential vasodilation of afferent arterioles with increases in GFR, renal blood flow, and natriuresis appears to favor the use of CCBs as a way of maintaining good renal function. However, a large body of experimental data suggests that increased renal plasma flow and GFR may accelerate the progression of glomerulosclerosis by increasing intraglomerular BP (Griffin et al., 1995).

In patients with renal damage, mixed effects have been seen. In patients with less than 500 mg per day albuminuria, dihydropyridines and verapamil reduce protein excretion as well as do ACEIs; in those with albuminuria greater than 500 mg per day, dihydropyridines do not reduce proteinuria, whereas verapamil and diltiazem do so equally as well as do ACEIs (Kloke et al., 1998). In the ongoing African-American Study of Kidney Disease and Hypertension, amlodipine did not slow the rate of decline of renal function in hypertensive blacks with renal insufficiency and heavy proteinuria as well as did the ACEI ramipril (Agodoa et al., 2001). Therefore, CCBs should be only added to an ACEI if needed to control hypertension in patients with renal insufficiency.

Additional Uses

Cardiovascular Diseases

Short-acting CCBs, particularly large doses of liquid nifedipine, have been shown to increase mortality when used after an acute MI (Furberg et al., 1995). Moreover, short-acting CCBs have also been shown to increase coronary events when used to treat hypertension (Psaty et al., 1995). However, long-acting CCBs do not share these dangers (Alderman et al., 1997). Data from a large RCT in elderly patients with systolic hypertension—the Systolic Hypertension in Europe Trial (Syst-Eur trial)—show equal protection with the dihydropyridine CCB nitrendipine, as previously was seen with diuretic-based therapy (Staessen et al., 1997). In this study, those patients on the CCB had 42% fewer strokes and 26% fewer coronary events than did those on the placebo, both highly significant reductions.

Coronary Heart Disease

CCBs are effective in the treatment of both classic angina pectoris and the less frequent vasospastic angina. Their effects in other types of CHD are generally favorable.

In the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial, 825 patients with angiographic evidence of coronary artery disease were randomly assigned to receive either amlodipine or placebo (Pitt et al., 2000a). After 36 months, the reduction in minimal diameter of the coronary arteries was identical in the two groups, whereas carotid atherosclerosis was slowed significantly in those given the CCB. There were no differences in rates of all-cause mortality or major cardiovascular events but fewer cases of unstable angina and coronary revascularization in those given amlodipine.

In another placebo-controlled RCT, amlodipine started 2 weeks before percutaneous transluminal coronary angioplasty did not reduce luminal loss but significantly reduced major adverse clinical events over the 4-month follow-up (Jørgensen et al., 2000).

In patients with stable angina, both short- and intermediate-acting nifedipine as monotherapy was associated with more episodes of increased angina than were seen with long-acting nifedipine (Stason et al., 1999). Opie (2000) has reviewed evidence that long-acting dihydropyridines and verapamil may be preferable to b-blockers in chronic stable effort-induced angina.

After Myocardial Infarction

Verapamil and, to a lesser extent, diltiazem have been found to influence favorably the clinical out-comes of patients recovering from non–Q-wave MI and hypertensive patients after MI who have preserved left ventricular function (Gibson and Boden, 1996). In a more recent trial of MI survivors treated with thrombolytic agents, diltiazem started within 36 to 96 hours of infarct onset did not reduce the cumulative incidence of cardiac death, nonfatal reinfarction, or refractory ischemia during a 6-month follow-up but did reduce all nonfatal cardiac events, especially the need for myocardial revascularization (Boden et al., 2000).

Heart Failure

Although adverse effects have been seen with both rate-slowing agents such as diltiazem (Kostis et al., 1997) and first-generation dihydropyridines such as nifedipine, benefit was noted among patients with severe CHF from nonischemic- (but not ischemic-) dilated cardiomyopathy given the second-generation agent amlodipine (Packer et al., 1996b). In their analysis of 17 studies of more than 2000 patients with CHF given dihydropyridines, de Vries et al. (2000) conclude: “The data do not support the use of dihydropyridines when primarily given as treatment for CHF. The results, however, suggest that these drugs can be safely given to patients with left ventricular dysfunction or CHF who need additional treatment for angina pectoris or hypertension.”

Left Ventricular Hypertrophy

CCBs have been found to be as effective as ACEIs in inducing regression of LVH (van Zwieten, 2000). In one of the few prospective comparative trials, amlodipine and lisinopril reduced left ventricular mass and improved diastolic function similarly in 166 newly diagnosed elderly hypertensives (Terpstra et al., 2001). These agents may be most effective in improving impaired coronary vasodilator reserve in those with LVH (Vogt and Strauer, 1995).

Arrhythmias

Verapamil and, to a lesser degree, diltiazem have been widely used to treat supraventricular tachyarrhythmias, particularly reentrant AV nodal tachycardia and atrial fibrillation (Abernethy and Schwartz, 1999).

Valvular Diseases

In asymptomatic patients with chronic aortic regurgitation, long-term use of nifedipine has delayed the need for operation (Levine and Gaasch, 1996). For most patients with chronic mitral regurgitation, Levine and Gaasch (1996) believe an ACEI to be preferable, although a short-term benefit has been seen with nifedipine

(Kelbæk et al., 1996).

Cerebrovascular Disease

The dihydropyridine nimodipine (Nimotop) has been approved for relief of vasospasm after sub-arachnoid hemorrhage (Feigin et al., 1998) but is of no benefit after acute ischemic hemispheric stroke (Kaste et al., 1994). In the Syst-Eur trial, nitrendipine provided a 42% reduction in the total stroke rate in elderly patients with systolic hypertension (Staessen et al., 1997).

Peripheral Vascular Disease

Verapamil was effective in the treatment of intermittent claudication over a 4-week trial (Bagger et al., 1997).

Primary Pulmonary Hypertension

Sustained improvement has been noted in 25% to 30% of patients with primary pulmonary hypertension given nifedipine, better results than were seen with verapamil or ACEIs (Rubin, 1997).

Other Diseases

CCBs have proven useful in the management of various conditions associated with muscular contraction (Fisher and Grotta, 1993), including Raynaud's phenomenon (Raynaud's Treatment Study Investigators, 2000) and preterm labor (Lockwood, 1997).

Side Effects

As is reviewed later in this chapter, serious consequences of the use of short-acting CCBs have been reported in observational studies involving diltiazem, nifedipine, and verapamil. Without rehashing the evidence, I believe most of it is confounded by the inherent problem of using these drugs in patients with underlying conditions, who thereby are more likely to get into trouble (Leader et al., 2001), and is further beclouded by the failure to ascertain actual drug use (Kaplan, 1996a, 1996b). Nonetheless, some associations have turned out to be valid. The association of short-acting CCBs and mortality after an MI is one (Alderman et al., 1997); their association with increased bleeding may be another (Zuccalá et al., 2000). As noted earlier, none of these claims has been documented with the use of long-acting CCBs, which induce distinctly different hemodynamic and hormonal responses than do the short-acting agents (Hamada et al., 1998).

In addition to these serious possible problems, milder side effects will preclude the use of these drugs in perhaps 10% of patients. Most side effects—headaches, flushing, local ankle edema—are related to the vasodilation for which the drugs are given (van Hamersvelt et al., 1996). With slow-release and longer-acting formulations, vasodilative side effects are reduced. It should be no surprise that, in a few patients, the antihypertensive effect of the short-acting agents, particularly liquid nifedipine, may be so marked as to reduce blood flow and induce ischemia of vital organs (Grossman et al., 1996). The side effects of the three major classes of CCBs differ considerably (Table 7-9).

Effect	Verapamil	Diltiazem	Dihydropyridines
Cardiovascular system			
Hypotension	+	+	++
Flush	+	-	++
Headache	+	+	++
Ankle edema	+	+	++
Palpitation	-	-	+
Conduction disturbances	++	+	-
Bradycardia	++	+	-
Gastrointestinal tract			
Nausea	+	+	+
Constipation	++	(+)	-

+ signs indicate the magnitude of the side effects; - sign indicates no effect.

TABLE 7-9. *Relative frequency of side effects of calcium channel blockers*

Verapamil

Constipation is the most common side effect, and AV block is the most serious one. To avoid conduction problems, the drug should generally be avoided in patients with sick sinus syndrome, second- or third-degree AV block, or CHF (Carruthers et al., 1989).

Diltiazem

The incidence of both gastrointestinal symptoms and conduction problems is lower with diltiazem, but this drug is best avoided in patients with the underlying conduction disturbances noted previously for verapamil (Abernethy and Schwartz, 1999).

Dihydropyridines

Vasodilative side effects are more common with the dihydropyridines but less so with the second generation of slower-release and longer-acting preparations. For example, headache was no more common with amlodipine than with placebo, and flushing was seen in only 2.4% of patients on the drug (Murdoch and Heel, 1991). On the other hand, dependent edema remains a relatively common problem, related to localized vasodilation and not generalized fluid retention (Iabichella et al., 1997). Interestingly, dependent edema was seen in 14.6% of women who took amlodipine but in only 5.6% of men (as compared with 5.1% and 1.4%, respectively, who were on placebo). If this condition bothers the patient, a diuretic will likely not help, and either a nondihydropyridine CCB or a drug from another class should be substituted (Weir et al., 2001). Combining a CCB with an ACEI reduces the development of pedal edema (Gradman et al., 1997).

Other Side Effects

Gingival hyperplasia has been noted, most commonly with dihydropyridines (Missouris et al., 2000). Eye pain, possibly due to ocular vasodilation, has been noted with nifedipine (Coulter, 1988). A wide spectrum of adverse cutaneous reactions, some quite serious, has been reported to occur rarely with various CCBs (Orme and da Costa, 1999).

Impotence seems rare, but 31 patients have been reported to develop gynecomastia (Tanner and Bosco, 1988).

Overdoses usually are manifested by hypotension and conduction disturbances and can usually be overcome with parenteral calcium and sympathomimetics (Abernethy and Schwartz, 1999).

Unfounded Concerns

Because calcium entry is involved in so many cellular functions, concerns have been voiced about other potential adverse effects of CCBs. Calcium metabolism seems little altered (Townsend et al., 1990). The secretion of various hormones is not affected other than a reduced adrenal steroid response to both adrenocorticotropic hormone and angiotensin (Favre et al., 1988; McDermott et al., 1990).

CCBs have no unfavorable effects on glucose homeostasis and do not decrease insulin sensitivity (Cabezas-Cerrato et al., 1997; Pollare et al., 1989b). CCBs tend to have no effects on serum lipids (Kasiske et al., 1995).

Although six cases of aplastic anemia were attributed to the intake of nifedipine (Laporte et al., 1998), no association with this condition and use of CCBs was found in a case-control analysis of a massive population (MW Myers et al., 2000).

Drug Interactions

A problem noted with most other classes of antihypertensive drugs—interference from NSAIDs—is usually not seen with CCBs (Celis et al., 2001). Another interaction has been noted with the dihydropyridines felodipine and nifedipine but not with amlodipine (Vincent et al., 2000): an increased plasma level and duration of action when taken along with grapefruit juice (Bailey et al., 2000) or Seville orange juice (Malhotra et al., 2001). Most other drug interactions with CCBs are of little consequence (Abernethy and Schwartz, 1999), except the possible major cost savings represented by the lower doses of cyclosporine needed with concomitant CCB therapy (Valantine et al., 1992).

Perspective on Use

As reviewed in Chapter 5, CCBs have been found to reduce stroke more but heart attacks less than other therapies while having similar effects on overall mortality (Blood Pressure Lowering, 2000). They work well and are usually well tolerated across the entire spectrum of hypertensives. They have some particular niches: coexisting angina and cyclosporine or NSAID use. If chosen, an inherently long-acting, second-generation dihydropyridine seems the best choice, because it will maintain better BP control in the critical early morning hours (Östergren et al., 1998) and on through the next day if the patient misses a daily dose (Leenen et al., 1996). Rate-slowing CCBs (e.g., verapamil or diltiazem) may be preferable in certain circumstances.

The phenomenal growth over the last 15 years of the use of CCBs for the treatment of hypertension (Fig. 7-1) may have been slowed by the numerous reports of problems with short-acting formulations. These reports do not establish any cause-and-effect relationship. A thorough review of all these claims by a committee of experts from the World Health Organization and International Society of Hypertension concluded: “The available evidence about the effects of calcium antagonists on the risks of CHD, cancer and bleeding does not establish the existence of beneficial or harmful effects” (Ad Hoc Subcommittee, 1997). A later review by Kizer and Kimmel (2001) concluded: “Initial reports of cancer, bleeding and suicide have been contradicted by subsequent data.” Moreover, these claims involved only short-acting CCBs, and the accumulating evidence fails to show that any of these purported problems apply to longer-acting formulations. Nonetheless, guilt by association will almost certainly cause some to avoid the long-acting agents as well. In addition, the multiple special indications for ACEIs, as detailed in the next section, have added to their allure.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

As detailed in Chapter 3 and depicted in Figure 7-12, there are four ways to reduce the activity of the renin-angiotensin system in humans. The first way, the use of b-blockers to reduce renin release from the juxtaglomerular cells, has been covered. The second way, the direct inhibition of the activity of renin, is being actively investigated with a variety of renin inhibitors. The third way is to inhibit the activity of ACE, which converts the inactive decapeptide angiotensin I (AI) to the potent hormone angiotensin II (AII; i.e., ACEIs). The fourth way is to use a competitive antagonist that attaches to the AII receptors and blocks the attachment of the native hormone. Multiple ARBs are now available and are beginning to challenge ACEIs.

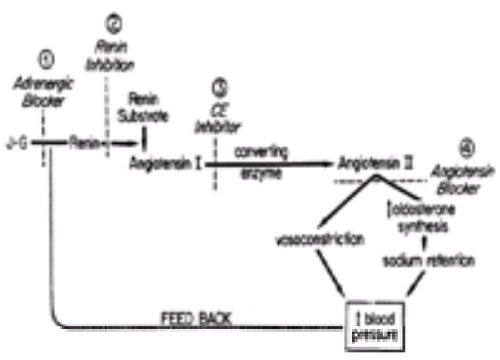


FIG. 7-12. The renin-angiotensin system and four sites where its activity may be inhibited. CE, converting enzyme; J-G, juxtaglomerular.

This section examines the use of ACEIs. Thereafter, the use of ARBs will be described.

Pharmacology

Peptides from the venom of the Brazilian viper *Bothrops jararaca* were discovered to potentiate the effects of bradykinin by inhibiting its degradation (Ferreira, 1965). Soon thereafter, Ng and Vane (1967) recognized that the same enzyme from the carboxypeptidase family could be responsible for both the conversion of AI to AII and the degradation of bradykinin. The nature of this ACE was identified by Erdös and coworkers in 1970 (Yang et al., 1970). Biochemists at the Squibb laboratories identified the first inhibitor for the ACE enzyme, teprotide or SQ20881 (Ondetti et al., 1971), which was shown to lower BP when given intravenously (Gavras et al., 1974). The Squibb group then identified the active site on the ACE and developed the first orally effective ACEI, captopril (Ondetti et al., 1977).

Three chemically different classes of ACEIs have been developed, classified by the ligand of the zinc ion of ACE: sulfhydryl, carboxyl, and phosphoryl (Table 7-10). Their different structures influence their tissue distribution and routes of elimination (Brown and Vaughan, 1998), differences that could alter their effects on various organ functions beyond their shared ability to lower the BP by blocking the circulating renin-angiotensin mechanism. Differences in tissue penetration of the ACEIs may result in different clinical effects (Anderson et al., 2000), but these have not yet been proved (Zisman, 1998).

Drug	U.S. trade name	Zinc ligand	Prodrug	Route of elimination	Duration of action (h)	Dose range (mg)
Benazepril	Lotensin	Carboxyl	Yes	Renal	24	5–40
Captopril	Capoten	Sulfhydryl	No	Renal	6–12	25–150
Ciliazapril	—	Carboxyl	Yes	Renal	24+	2.5–5.0
Enalapril	Vasotec	Carboxyl	Yes	Renal	18–24	5–40
Fosinopril	Monopril	Phosphoryl	Yes	Renal-hepatic	24	10–40
Lisinopril	Prinivil, Zestril	Carboxyl	No	Renal	24	5–40
Moexipril	Univasc	Carboxyl	Yes	Renal	12–18	7.5–30.0
Perindopril	Aceon	Carboxyl	Yes	Renal	24	4–16
Quinapril	Accupril	Carboxyl	Yes	Renal	24	5–80
Ramipril	Altace	Carboxyl	Yes	Renal	24	1.25–20.0
Spirapril	—	Carboxyl	Yes	Hepatic	24	12.5–50.0
Trandolapril	Mavik	Carboxyl	Yes	Renal	24+	1–8

TABLE 7-10. *Characteristics of angiotensin-converting enzyme inhibitors*

Pharmacokinetics

As seen in Table 7-10, most ACEIs are prodrugs, esters of the active compounds that are more lipid-soluble, so that they are more quickly and completely absorbed. Captopril, an active drug, reaches a peak blood level within 30 to 60 minutes; enalaprilat, the active metabolite of enalapril, peaks at about 4 hours. Although there are large differences in bioavailability, these seem to make little difference in the clinical effects, likely because of the variable degrees of binding to ACE, tissue penetration, and elimination that contribute to the overall effects (Komajda and Wimart, 2000).

Most ACEIs, except fosinopril and spirapril, are eliminated through the kidneys, having undergone variable degrees of metabolism. Fosinopril has a balanced route of elimination, with increasingly more of the drug removed through the liver as renal function decreases (Hui et al., 1991).

Mode of Action

As seen in Figure 7-12, the most obvious manner by which ACEIs lower the BP is to reduce the circulating levels of AII markedly, thereby removing the direct vasoconstriction induced by this peptide. At the same time, the activity of ACE within vessel walls and multiple tissues, including brain and heart, is inhibited, apparently to variable degrees by different ACEIs (Brown and Vaughan, 1998).

Although the presence of the complete reninangiotensin system within various tissues, including vessel walls, heart, and brain, is certain, the role of these tissue renin-angiotensin systems in pathophysiology remains uncertain, as does the contribution of inhibition of tissue ACE to the antihypertensive effects of ACEIs.

Moreover, nonclassical pathways may be involved in the elaboration of AII, involving either nonrenin effects on angiotensinogen or non-ACE effects on AI (Fig. 7-13). Because ACEIs block only AII production via the classical pathway, there could then be additional effects of ARBs. On the other hand, some of the effects of ACEIs may be mediated via their inhibition of the breakdown of bradykinin (Erdös et al., 1999), with an additional contribution from kinin stimulation of nitric oxide production (Burnier and Brunner, 2000). NSAIDs clearly reduce the antihypertensive effect of ACEIs, likely by inhibiting vasodilatory prostaglandin production (Polónia et al., 1995).

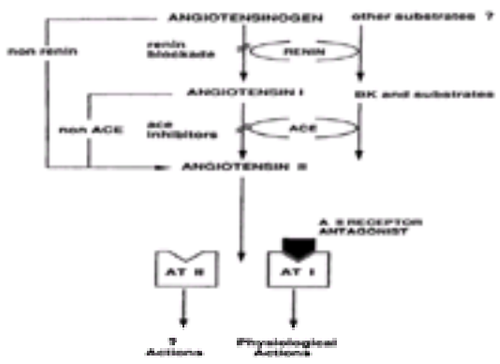


FIG. 7-13. Theoretic biochemical and physiologic consequences of blocking the renin-angiotensin system at different steps in the pathway. ACE, angiotensin-converting enzyme; AT, angiotensin; BK, bradykinin. (Modified from Johnston CI, Burrell LM. Evolution of blockade of the renin-angiotensin system. *J Hum Hypertens* 1995;9:375–380.)

Regardless of the contributions of various other mechanisms beyond the reduction in AII levels, the lower AII levels certainly play a major role. In addition to the relief of vasoconstriction, multiple other effects likely contribute to their antihypertensive effect:

- A decrease in aldosterone secretion (Gavras et al., 1977), which may cause natriuresis or at least a lack of reactive renal sodium retention as the BP falls.
- An increase in the activity of the 11b-hydrox-ysteroid dehydrogenase-2 enzyme, which could increase renal sodium excretion by protecting the nonselective mineralocorticoid receptor from cortisol (Ricketts and Stewart, 1999).
- Blunting of the expected increase in sympathetic nervous system activity typically seen after vasodilation (Lyons et al., 1997). As a result, heart rate is not increased and cardiac output does not rise, as is seen with direct vasodilators such as hydralazine. However, neither sympathetic nerve traffic (Grassi et al., 1998) nor other indices of sympathetic nervous system activity (Lee et al., 1999) are suppressed.
- Suppression of endogenous endothelin secretion (Brunner and Kukovetz, 1996).
- Improvement in endothelial dysfunction (Goto et al., 2000; Taddei et al., 1998). At least in patients with renovascular disease, the improvement in vascular function did not relate to either lowering of BP or known AII-mediated effects (van Ampting et al., 2001).

As a consequence of these multiple effects, ACE inhibition results in a dampening of arterial wave reflections and increased aortic distensibility (London et al., 1996). These hemodynamic improvements contribute to the reversal of hypertrophy both in the heart and vasculature that may be quantitatively greater with ACEIs than with other antihypertensive agents (Rizzoni et al., 1997). Beyond the hemodynamic effects, captopril has been found to inhibit angiogenesis (Volpert et al., 1996). However, the use of an ACEI did not prevent restenosis after coronary balloon angioplasty (Multicenter European Research Trial, 1992).

ACEIs are also venodilators (Zarnke and Feldman, 1996), and their effect may be responsible for their ability to reduce the accumulation of ankle edema seen with CCBs when the two agents are combined (Gradman et al., 1997).

One additional feature of ACEIs that has clinical relevance is their ability to shift the lower limit of cerebral autoregulation toward lower BP levels (Lartaud et al., 1994). As a consequence, patients with low BP given an ACEI, as in the treatment of heart failure, do not usually develop symptoms of cerebral hypoperfusion (Paulson et al., 1986) and CBF is maintained even as systemic BP is lowered (Dyker et al., 1997).

Ancillary Beneficial Effects

Regardless of how ACEIs lower the BP, they do so in a manner that tends to protect the function of two vital organs—the heart and the kidneys.

Cardiac Effects

ACEIs provide multiple benefits:

- Regression of LVH and myocardial fibrosis (Brilla et al., 2000)
- Improvement in coronary flow reserve (Schwartzkopff et al., 2000)
- Attenuation of sympathetic-mediated coronary vasoconstriction (Antony et al., 1996)
- Decreases in plasminogen activator inhibitor-1 activity (Brown et al., 1998)
- Prevention of nitrate tolerance, likely best with captopril (Pizzulli et al., 1996)
- Reduction in mortality after acute MI, most obvious in those with evidence of heart failure (Cleland et al., 1997) but probable in all high-risk patients (O'Keefe et al., 2001)
- Relief of acute and chronic CHF by altered remodeling and sustained reduction in preload and afterload (Flather et al., 2000)
- In animal models, inhibition of atherosclerosis even without reducing BP or potentiating bradykinin (Keidar et al., 2000)

With the impressive protection against morbidity and mortality provided by addition of ramipril to the therapy for high-risk patients in the Heart Outcomes Prevention

Evaluation (HOPE) (2000a), ACEI therapy has been recommended as routine therapy for all patients with atherosclerotic disease (O'Keefe et al., 2001).

Renal Effects

The kidneys may also be specially protected by the preferential vasodilatation of the efferent arterioles provided by reduction of AII, thereby reducing intraglomerular pressure. As is further described in Chapter 9, this action of ACEIs may give them a unique protective effect in patients susceptible to progressive damage from glomerular hypertension, an effect that extends to normotensive diabetics (Mathiesen et al., 1999), and ACEIs are able to slow progression of proteinuric nephropathy (Jafar et al., 2001).

In experimental animals, the renal hemodynamic effects of ACE inhibition appear to involve the action of kinins (Mathiesen et al., 1999), opening the possibility that these effects would not be seen with ARBs. However, Mogensen et al. (2000) found no differences in various indices of renal protection between an ACEI and an ARB in patients with diabetic renal disease.

Insulin Sensitivity

Captopril has been shown to increase sensitivity to insulin and to lower plasma insulin levels (Pollare et al., 1989a). Nonsulfhydryl ACEIs may not share this effect (Haenni et al., 1997). Ramipril reduced the incidence of diabetes in the HOPE trial (Yusuf et al., 2001).

Differences among Angiotensin-Converting Enzyme Inhibitors

Although the distinct differences in tissue distribution and routes of elimination between various ACEIs could be reflected in different antihypertensive potencies and ancillary properties, in most obvious ways all ACEIs seem quite alike (Brown and Vaughan, 1998). The most widely touted difference—the presence of a sulfhydryl group in captopril—may be responsible for some additional effects, including scavenging of free radicals (Andreoli, 1993), attenuating lipid peroxidation (Liu et al., 1992), and improving insulin sensitivity.

Efficacy

A rather remarkable turnabout has occurred since 1979 when captopril was approved only for use in patients with severe hypertension unresponsive to other agents. ACEIs are now included among the drugs recommended for initial monotherapy of patients with a variety of comorbid conditions accompanying hypertension (Guidelines Subcommittee, 1999; Joint National Committee, 1997). This turnabout reflects the use of smaller doses, the recognition of equal efficacy but apparently fewer side effects than are seen with other classes, and the provision of some special advantages not provided by other drugs now available.

Monotherapy

An immediate fall in BP occurs in approximately 70% of patients given captopril, and the decrease is sometimes rather precipitous (Postma et al., 1992). Such a dramatic fall is more likely in those with high renin levels, particularly if they are volume-depleted by prior dietary sodium restriction or diuretic therapy.

Black hypertensives, with lower renin levels as a group, have been found to respond less well to ACEIs than do white hypertensives (Materson et al., 1993; Saunders et al., 1990). Younger patients tend to respond better than elderly patients (Morgan et al., 2001).

As expected, patients with high-renin forms of hypertension (e.g., renovascular hypertension) may respond particularly well to ACEIs, but the removal of AII's support of perfusion to the ischemic kidney may precipitously reduce renal function, particularly in those with bilateral stenoses (Hricik et al., 1983) (see Chapter 10). If such patients are excluded, ACEIs are usually effective and well tolerated in patients with renal insufficiency. Renal function may worsen if the BP is reduced too much (Toto et al., 1991) or in the presence of heart failure (Kalra et al., 1999). Renal protection may not be provided for patients with the *DD* ACE genotype that is accompanied by higher plasma ACE levels (van Essen et al., 1996).

Sublingual captopril is effective in lowering severe hypertension (Angeli et al., 1991) but is just as likely as sublingual nifedipine to lower the BP too much too quickly, so it too should be used rarely, if ever, for this purpose (see Chapter 8).

Combination Therapy

The addition of a diuretic, even in as low a dose as 6.25 mg HCTZ, will enhance the efficacy of an ACEI (Cheng and Frishman, 1998), normalizing the BP of another 20% to 25% of patients with mild to moderate hypertension more effectively than would raising the dose of the ACEI (Townsend and Holland, 1990). The marked additive effect of a diuretic likely reflects the ACEI blunting of the reactive rise of AII that usually occurs with diuretic use and that opposes the antihypertensive effect of the diuretic. Combinations of an ACEI and a CCB provide additive effects (de Leeuw et al., 1997) and likely reduce the prevalence of pedal edema seen with CCBs alone (Gradman et al., 1997).

Use in Concomitant Conditions

Renal and Heart Disease

As noted in the section Ancillary Beneficial Effects (under Angiotensin-Converting Enzyme Inhibitors), ACEIs may provide special benefits to patients with renal disease, particularly from diabetic nephropathy, or various cardiac conditions, including CHF and following an acute MI. Cardiac patients should not be denied their use because of concomitant moderate renal insufficiency (Frances et al., 2000). Because even small doses of aspirin may blunt their benefits, larger doses of ACEIs may be needed in such patients. Although caution in the use of ACEIs is needed in all patients with extensive atherosclerosis because of their higher prevalence of renovascular disease, in a substudy of the HOPE trial involving 732 patients, those given ramipril had a slower rate of progression of carotid atherosclerosis than did those given placebo (Lonn et al., 2001). Moreover, ramipril reduced the excess risk for cardiovascular events in the patients enrolled in the HOPE trial who had mild renal insufficiency at baseline (Mann et al., 2001).

Other Conditions

ACEIs improve walking distance in hypertensive patients with *intermittent claudication* (McInnes, 1994). Lisinopril was found to provide a significant prophylaxis against *migraine* (Schrader et al., 2001).

Dosage

Neither the degree nor the duration of the antihypertensive efficacy of ACEIs can be predicted by their effect on blood ACE or AII levels. The major difference between them is the duration of action.

Captopril

Initially, captopril was usually given in doses that are now known to be inordinately high, up to 300 mg three times per day. With more experience, doses have come down. In a VA Cooperative Study (1984), the response was as good with 12.5 mg three times per day as with 25 or 50 mg three times per day. There is probably no need for using more than 150 mg per day.

A starting dose of 25 mg twice a day seems appropriate for most patients. Patients with renal insufficiency or CHF or who are on prior diuretic therapy should be started on less, as little as 6.25 mg.

Enalapril

The effect of usual doses of enalapril may not last for a full 24 hours (Diamant and Vincent, 1999), so the drug should be given twice daily. In a controlled study, little additional response on BP was noted when doses were increased from 10 to 40 mg per day (Salvetti and Arzilli, 1989).

Other Angiotensin-Converting Enzyme Inhibitors

All the other ACEIs usually provide full 24-hour effectiveness with one dose per day, particularly perindopril (Tan and Leenen, 1999) and trandolapril (Meredith, 1996).

Side Effects

With large doses of captopril in patients with severe hypertension, many of whom also had renal insufficiency, a high incidence of side effects was initially reported. As smaller doses have been used in patients with normal renal function, the incidence of side effects has fallen significantly. For example, the incidence of neutropenia was 7.2% in patients with collagen vascular disease and impaired renal function and 0.4% in patients with renal insufficiency from other causes but only 0.02% in patients with normal renal function (Warner and Rush, 1988).

The recognized side effects of ACEIs logically can be divided into three types: (a) those anticipated from their specific pharmacologic actions, (b) those probably related to their chemical structure, and (c) nonspecific effects, as seen with any drug that lowers the BP.

The relative incidence of side effects may differ somewhat among the various ACEIs but, in general, they are fairly close. However, with careful assessment of various quality-of-life (QOL) measures, equipotent doses of captopril and enalapril had opposite effects—captopril positive, enalapril negative (Testa et al., 1993).

Effects Anticipated from Pharmacologic Actions

First-Dose Hypotension

An immediate fall in mean arterial BP of more than 30% was seen in 3.3% of 240 hypertensive patients given 25 mg captopril (Postma et al., 1992). The likelihood of such an abrupt fall is less with other ACEIs, which are prodrugs and have a slower onset of action (Table 7-10).

Elevation of Plasma Potassium

The inhibition of AII-mediated aldosterone secretion blunts potassium excretion, particularly in diabetic patients with underlying renal insufficiency (Ahuja et al., 2000). Potassium levels may rise even more if an ACEI is combined with potassium-sparing agents or potassium supplements (Ray et al., 1999).

Hypoglycemia

Perhaps as a reflection of increased insulin sensitivity, ACEI use has been accompanied by hypoglycemia both in insulin-dependent and non–insulin-dependent diabetics (Herings et al., 1995).

Interference with Erythropoietin

ACEIs have been claimed to interfere with the action of erythropoietin in correcting the anemia of renal transplant recipients (Gossman et al., 1996) (see Chapter 9).

Deterioration of Renal Function

With the high doses of captopril used initially, an immune-complex glomerulopathy was reported (Hoorntje et al., 1980) but later was shown to reflect preexisting renal damage (Captopril Collaborative Study Group, 1982).

Most subsequent reports of acute loss of renal function involved patients with CHF, volume depletion (McMurray and Matthews, 1987), or renal artery stenoses, either bilaterally or in a solitary kidney (Hricik et al., 1983). Rarely, acute renal failure may occur, which may require dialysis (Wynckel et al., 1998). However, acute increases of serum creatinine of up to 30% that stabilize within the first 2 months of ACEI therapy are associated with *better* long-term renoprotection (Bakris and Weir, 2000), and so such rises should not lead to withdrawal of ACEI therapy.

Pregnancy

ACEIs are contraindicated during the second and third trimesters of pregnancy, because they cause fetal injury and death (Shotan et al., 1994). No definite evidence of ACEI fetal damage has been noted among 48 infants born to mothers who took an ACEI during the first trimester (Feldkamp et al., 1997).

Cough and Bronchospasm

A dry, hacking, nonproductive, and sometimes intolerable cough is the most frequent side effect of ACEI therapy; bronchospasm may be the second most frequent. In a controlled cohort study of 1,013 patients on an ACEI and 1,017 on lipid-lowering drugs, cough developed in 12.3% and bronchospasm in 5.5% of patients on an ACEI versus 2.7% and 2.3%, respectively, in those on the lipid-lowering drugs (Wood, 1995). However, the frequency of complaints of cough was some ten times greater than for bronchospasm in Sweden (Lunde et al., 1994).

Either problem may begin soon after the start of therapy but, in Wood's (1995) study, bronchospasm was not usually associated with cough. An increase in bradykinin has been assumed to be the mechanism for the cough (Yeo et al., 1995), and a genetic polymorphism of the bradykinin b_2-receptor has been found in a higher proportion of patients who have an ACEI-related cough (Mukae et al., 2000). Other mediators such as substance P and neurokinin A may be responsible (Tan et al., 1997).

Cough is more common in women (Shah et al., 2000) and blacks (Elliott, 1996) and was reported in almost half of Chinese patients (Woo and Nicholls, 1995). It usually goes away in a few weeks after the drug is withdrawn and usually recurs with reexposure to an ACEI (Charlon et al., 1995). Although the cough may be effectively treated with inhaled sodium cromoglycate (Hargreaves and Benson, 1995) or aspirin (Tenenbaum et al., 2000), the easiest way to resolve the problem is to replace the ACEI with an ARB.

Angioedema and Anaphylaxis

Angioedema occurs in 0.1% to 0.2% of patients given an ACEI, usually within hours but sometimes after prolonged use (Pillans et al., 1996). Recurrent episodes, some with visceral involvement (Mullins et al., 1996), may not be attributed to ACEI use until years after they are begun (Brown et al., 1997). Anaphylactoid reactions have been seen during dialysis and apheresis in patients on ACEIs, presumably because of an inability to inactivate bradykinin generated by contact of blood with negatively charged surfaces (Davidson et al., 1994).

Hypotension may occur when blood is transfused through a bedside leukoreduction filter to patients on an ACEI, presumably by generation of bradykinin (Quillen, 2000).

Effects Related to Chemical Structure

Effects related to chemical structure may be more common with captopril than with the nonsulfhydryl ACEIs, because most are also seen with other sulfhydryl-containing drugs such as penicillamine (Hammarström et al., 1991). Most, but not all, patients who experience one of these reactions while on captopril can be safely crossed over to another ACEI (Jackson et al., 1988).

Taste Disturbance

Although usually of little consequence and self-limited with continued drug intake, taste disturbance may be so bad as to interfere with nutrition. It appears to be related to the binding of zinc by the ACEI (Abu-Hamdan et al., 1988).

Rash

The rash is usually a nonallergic, pruritic, maculopapular eruption that appears during the first few weeks of therapy and may disappear despite continuation of the ACEI. Serious skin reactions including Schönlein-Henoch purpura have been reported (Gonçalves et al., 1998).

Leukopenia

Leukopenia probably occurs exclusively in patients with renal insufficiency (Cooper, 1983), particularly those with underlying immunosuppression either from a disease or from a drug.

Nonspecific Side Effects

ACE activity is present in intestinal brush border, and adverse gastrointestinal effects have been reported with ACEI use (Edwards et al., 1992). Other rare effects include pancreatitis (Roush et al., 1991) and cholestatic jaundice (Nissan et al., 1996).

ACEIs have no major effects on cognitive function (Ebert and Kirch, 1999) and are “lipid-neutral” (Kasiske et al., 1995), escaping some of the common side effects of other drugs. Headache, dizziness, fatigue, diarrhea, and nausea are listed in reviews but are seldom problems. Sudden withdrawal does not usually lead to a rebound (Vlasses et al., 1981). Overdose causes hypotension that should be easily managed with fluids and, if needed, dopamine (Lip and Ferner, 1995b).

Perspective on Use

Captopril, when first introduced for use in severe hypertensives and in high doses, earned a bad reputation that was quickly overcome. As appropriately lower doses were used and found to be as effective as other drugs, often with fewer side effects, captopril and then enalapril became increasingly popular. Over the last few years, many more ACEIs have been marketed, most with the added advantage of longer duration of action, allowing for once-daily dosing.

As ACEIs have been used in various situations, three places have been recognized wherein they provide special benefits beyond those provided by other agents: relief of acute and chronic heart failure, prevention of remodeling and progressive ventricular dysfunction after MI, and slowing of glomerular sclerosis in diabetic and other nephropathies. As a result, the 1997 Joint National Committee report (JNC-6) and the 1999 World Health Organization and International Society of Hypertension guidelines (Guidelines Subcommittee, 1999) specifically recommend ACEIs for initial therapy in hypertensives with these concomitant conditions. Beyond these specific indications, the evidence from the HOPE trial has led to the recommendation that an ACEI be given to all patients at high risk for CHD, whether hypertensive or not.

Even as ACEIs have become increasingly popular, their popularity has been threatened by the introduction of ARBs, agents that act at a more distal site of the renin-angiotensin system (Fig. 7-13).

ANGIOTENSIN II–RECEPTOR BLOCKERS

Even before ACEIs were available, a peptidic antagonist of AII receptors, saralasin, was shown to lower BP (Brunner et al., 1973). However, its use was limited by the need for intravenous administration and its pressor effect in low-renin patients resulting from its partial agonist effects (Case et al., 1976). Subsequently, the AII receptor was found to have at least two major subtypes, with the type 1 (AT_1) receptor mediating most of the physiologic roles of AII (Timmermans et al., 1993). The signaling mechanisms and functions of these receptor subtypes are different, and they may exert opposite effects on cell growth and BP regulation (Horiuchi et al., 1999). Agents that selectively block the AT_1-receptor have been synthesized and marketed for the treatment of hypertension. Losartan was the first, and now five more have been approved for use in the United States (Table 7-11).

Drug	Trade name (Supplier)	Half-life (h)	Active metabolite	Daily dosage (mg)
Candesartan	Atacand (AstraZeneca)	3–11	Yes	8–32 in 1 dose
Eprosartan	Teveten (Smith Kline Beecham)	5–7	No	400–800 in 1–2 doses
Irbesartan	Avapro (Bristol-Myers Squibb, Sanofi)	11–15	No	150–300 in 1 dose
Losartan	Cozaar (Merck)	2 (6–9)	Yes	50–100 in 1–2 doses
Telmisartan	Micardis (Boehringer Ingelheim)	24	No	40–80 in 1 dose
Valsartan	Diovan (Novartis)	9	No	80–320 in 1 dose

TABLE 7-11. *Angiotensin II–receptor blockers*

Mechanisms of Action

ARBs displace AII from its specific AT_1-receptor, antagonizing all of its known effects and resulting in a dose-dependent fall in peripheral resistance and little change in heart rate or cardiac output (Burnier and Brunner, 2000). As a consequence of the competitive displacement, circulating levels of AII increase while at the same time the blockade of the renin-angiotensin mechanism is more complete, including any AII that is generated through pathways that do not involve ACE (Fig. 7-13). No obvious good or bad effects of the increased AII levels have been noted (along with the higher renin levels, as also seen with ACEIs). However, chronic stimulation of AII type 2 receptors could have effects not now recognized (Horiuchi et al., 1999).

Differences between Angiotensin II– Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors

The major obvious difference between ARBs and ACEIs is the absence of an increase in kinin levels that may be responsible for some of the beneficial effects of ACEIs and likely even more of their side effects. Direct comparisons between the two types of drugs show few differences in antihypertensive efficacy, but cough is not provoked by the ARB (Tanser et al., 2000), although angioedema (Warner et al., 2000) and ageusia (Schlienger et al., 1996) have been reported with losartan. Losartan has a uricosuric effect that is not seen with other ARBs (Würzner et al., 2001). It is still uncertain that there are additive effects of an ARB with an ACEI, each of them at their maximally effective dose.

As seen with ACEIs, ARBs have been found to improve endothelial dysfunction and correct the altered structure of resistance arteries in patients with hypertension (Schiffrin et al., 2000). The greater degree of correction in the study by Schiffrin et al. (2000) with the ARB losartan compared to what these same investigators

previously reported with an ACEI (Schiffrin et al., 1994) prompted Hollenberg (2000) to suggest a significant non–ACE-dependent pathway in the arteries. Hollenberg et al. (1998) has previously found evidence for non–ACE-dependent conversion of AI to AII within the kidney. These tentative data led Hollenberg et al. (1998) to conclude: “Ang[iotensin] II antagonists [ARBs] have much greater potential for blocking the renin-angiotensin system than does ACE inhibition—with implications for therapeutics.”

However, as Hollenberg (2000) later admitted, “Such a conclusion must be tentative until an Ang[iotensin] II antagonist [ARB] and an ACEI are compared head-to-head in a proper randomized trial.”

Efficacy and Dosage

In the recommended doses (Table 7-11), all six currently available ARBs have comparable anti-hypertensive efficacy, and all are potentiated by addition of a diuretic (Conlin et al., 2000b). The dose-response curve is fairly flat for all, although increasing doses of candesartan show an increasing effect (Lacourcière and Asmar, 1999). Moreover, in this study, the effect of candesartan persisted for 36 hours after a purposely missed dose, whereas the effect of losartan was largely dissipated after 12 hours.

Others have found that a single daily dose of 50 mg losartan does not provide as complete 24-hour efficacy as do single daily doses of the other ARBs (Fogari et al., 2000). However, either the 100-mg dose or the combination of losartan with HCTZ does provide full 24-hour efficacy (Weber et al., 1995).

ARBs may be combined with other agents for additive effects (MacGregor et al., 2000). Multiple studies have shown additive effects when submaximal doses of an ARB are added to sub-maximal doses of an ACEI (Azizi et al., 2000; Fogari et al., 1999a). However, such additive effects have not been reported when either agent is added to a maximally effective dose of the other.

Ancillary Beneficial Effects

Renal Effects

ARBs are effective in the presence of renal insufficiency (Toto et al., 1998) and reduce proteinuria (Taal and Brenner, 2000). Data from three placebo-controlled trials (Brenner et al., 2001; Lewis et al., 2001; Parving et al., 2001), two using irbesartan, the third losartan—have shown 20% to 30% reductions in progression of renal damage in type II diabetics with nephropathy. Therefore, ARBs can be recommended for renoprotection. Moreover, ARBs may be safer in patients with renal insufficiency: Less of a rise in serum potassium was seen in patients with a mean GFR of 65 mL per minute per 1.73 m^2 who were given valsartan (potassium increase, 0.12 mEq per L above baseline) than in those given lisinopril (potassium increase, 0.28 mEq per L above base-line) (Bakris et al., 2000a).

Cardiac Effects

Prior concerns that ARBs did not induce regression of LVH (Himmelmann et al., 1996) have been shown not to be valid, and significant regression of LVH has been seen (Dahlöf, 2001).

The effectiveness of ARBs in heart failure and after MI has not yet been documented. The preliminary results of a comparison between losartan and captopril found an unexpected lower mortality in those given the ARB (Pitt et al., 1997). However, when this trial, the Evaluation of Losartan in the Elderly, was expanded, there were no significant differences in outcomes, although the ARB was better tolerated (Pitt et al., 2000b). The investigators concluded that ACEIs should remain the initial treatment for heart failure, with ARBs used only when ACEIs are not tolerated. In their commentary about this trial, Velazquez and Califf (2000) state:

> The results of the trial, as the investigators correctly state, should not tempt clinicians to offer their patients losartan as a more tolerable, equally effective alternative to captopril. The data are insufficiently strong for the claim that losartan and captopril are equivalent, because the confidence intervals cannot exclude the possibility of losartan being up to 5% better or 35% worse than captopril.

As with renal disease, the addition of an ARB to an ACEI may provide additional benefit (Baruch et al., 1999). Here again, larger and longer controlled trials will, hopefully, put the ARBs in their rightful place as cardioprotective agents (Struckman and Rivey, 2001).

Side Effects

Whether or not they are more effective than ACEIs, ARBs are easier to take. In double-blind clinical trials with losartan involving 2,900 hypertensives, side effects were generally no greater than with placebo, and the agent was better tolerated than other antihypertensive agents (Goldberg et al., 1995). Fetal toxicity (Saji et al., 2001), hyperkalemia, hypotension, and renal impairment will almost certainly be occasionally noted, because they are expected consequences of blockade of the renin-angiotensin mechanism but, as yet, no major surprises have surfaced. Somewhat surprisingly, those who develop angioedema on an ACEI may also do so on an ARB (Warner et al., 2000).

Perspective on Use

As reflected in the fast growth in the use of ARBs (Fig. 7-1), they are surely being prescribed for many more patients than the 10% or so of those who are intolerant of an ACEI. With the intensively competitive market for the six (or more) of these agents now being heavily promoted, their use will surely continue to grow. However, caution is advised: Additional outcome data are needed to know whether they are as good as the proven ACEIs. All current expert guidelines recommend ARBs only for those who should receive an ACEI but are intolerant, usually from cough. Despite the enthusiasm of many (Carson, 2000; Jamerson, 2000), patience is still prudent. Many outcome trials now in progress will provide evidence of their value beyond that found in type 2 diabetic nephropathy (Burnier, 2001).

DRUGS UNDER INVESTIGATION

Renin Inhibitors

Inhibitors of the action of renin to cleave the decapeptide AI from angiotensinogen include some that must be given intravenously, such as enalkiren (A-64662), and orally effective agents including Ro 42-5892 (Remikiren) and A72517 (Zankiren) (van Paassen et al., 2000). These agents are attractive not only because they can inhibit the production of AI and AII but also because they prevent the reactive rise in renin release that follows the use of ACEIs and ARBs. Whether any will become available for clinical use remains to be seen.

Vasopeptidase Inhibitors

The most exciting new class of drugs that likely will be available in the near future is vasopeptidase inhibitors, single molecules that simultaneously inhibit ACE and the neutral endopeptidase (NEP), which normally degrades a number of endogenous natriuretic peptides. Thereby, the effects of an ACEI—decreases in AII and increases in bradykinin—are combined with increases in natriuretic peptides (Burnett, 1999) (Fig. 7-14). The most widely studied of these agents is omapatrilat (Vanlev) (Rouleau et al., 2000), but a number of others are being investigated, including fasidotril (Laurent et al., 2000) and sampat rilat (Norton et al., 1999) as well as some agents that just inhibit the NEP enzyme [e.g., candoxatril (Northridge et al., 1999) and ecadotril (O'Connor et al., 1999)].

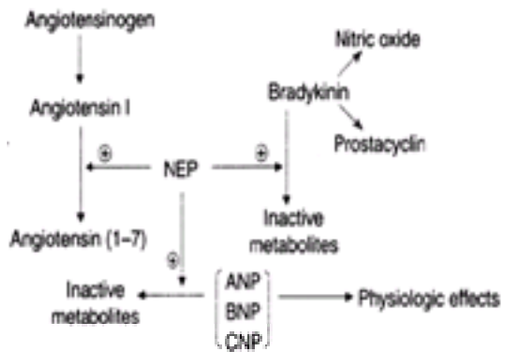


FIG. 7-14. Major components of the natriuretic peptide system. ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, c-type natriuretic peptide; NEP, neutral endopeptidase. [Modified from Burnett JC Jr. Vasopeptidase inhibition: a new concept in blood pressure management. *J Hypertens* 1999; 17(Suppl 1):S37–S43.]

The obvious attraction of the combined ACE and NEP inhibitors is the ability to have effects on both high and low renin states while providing a natriuresis without activating the renin system as do traditional diuretics (Walters and Reid, 2000). Initial clinical studies in patients with hypertension (Ferdinand et al., 2001 ; Levine et al., 2000) or heart failure (Rouleau et al., 2000 ; Troughton et al., 2000) have been favorable.

However, not surprisingly, the high levels of bradykinin induced by these agents (at least in the doses used in the initial trials) have led to a disturbing incidence of severe angioedema, so that the expected approval of omapatrilat has been delayed while additional studies are done with lower starting doses (Messerli and Nussberger, 2000).

Other Agents

Ketanserin

5-Hydroxytryptamine (5-HT), or serotonin, is a central and peripheral neurotransmitter that is involved in the regulation of BP. Ketanserin is a selective 5-HT_2-receptor antagonist with additional a_1-adrenergic receptor–blocking effects that lowers the BP in humans (Robertson, 1990). Ketanserin likely will not be introduced as an antihypertensive in the United States because of its proarrhythmic effect.

Urapidil

Urapidil is thought to activate 5-HT_{1A} receptors in the CNS, thereby decreasing the firing of serotoninergic neurons and reducing sympathetic nervous activity much like a_1-adrenergic receptor blockers do (van Zwieten, 1992).

Dopamine Agonists

Dopamine, the precursor of norepinephrine, induces vasodilation and lowers the BP (Goldberg, 1974). Exogenous dopamine also acts on b_1-receptors to stimulate the heart and on a_1- and a_2-receptors to cause vasoconstriction, so that it cannot be used to treat hypertension. Carmoxirole is a selective agonist for presynaptic peripheral dopamine-2 receptors that provides antihypertensive action by inhibition of noradrenaline release from sympathetic nerve endings (Haeusler et al., 1992). Fenoldopam is available as a parenteral agent with renal vasodilating effects for hypertensive crises (see Chapter 8).

The ergot derivative dihydroergotoxine has a modest antihypertensive effect that may be induced by a dopaminergic mechanism (Mercuro et al., 1992).

Potassium Channel Openers

Pinacidil, nicorandil, and cromakalim are representatives of drugs that vasodilate by opening potassium channels and enhancing potassium efflux from vascular smooth muscle cells (Ligtenberg et al., 1996).

Scopolamine

Transdermal scopolamine lowered BP by increasing parasympathetic activity (Vesalainen et al., 1998).

Drugs for the Far Future

The drugs just described are in varying stages of clinical investigation. Others are likely further away, including

- Endothelin receptor antagonists (Wenzel et al., 2001)
- Vasopressin receptor antagonists (Burrell et al., 1994)
- Endothelial protectors, including endotheliumderived relaxing factors (Burrell and Johnston, 1995)
- Transcription-modulating drugs (Kurtz and Gardner, 1998)
- Antisense gene therapy (Pachori et al., 2001)

Conclusion

A number of different drugs are under investigation. Time—and, in the United States, the U.S. Food and Drug Administration—will tell which of them will become available for clinical use. More drugs will be available, probably in rate-controlled forms, so that a single capsule or a patch may provide smooth control over many days. In the meantime, proper use of what is available will control BP in virtually every hypertensive patient.

GENERAL GUIDELINES FOR DRUG CHOICES

Now that the various drugs available to treat hypertension have been described, an attempt will be made to put them into a framework for clinical use, providing general guidelines for the subsequent section on how individual choices of therapy are best determined. First, the various classes will be compared, both as to their relative effectiveness in reducing hypertension-related morbidity and mortality and as to their likelihood of evoking significant adverse effects. Then two important pharmacologic characteristics of all drugs will be considered: their dose-response relationship and their duration of action, as these, too, enter into the decision for individual choices of therapy.

Comparisons between Drugs: Efficacy

Group Trials of Efficacy

The individual practitioner's choice of drug is often based on perceived differences in efficacy in lowering BP and the likelihood of side effects. In fact, overall antihypertensive efficacy varies little between the various available drugs; to gain U.S. Food and Drug Administration approval for marketing in the United States, the drug must have been shown to be effective in reducing the BP in a large portion of the 1,500 or more patients given the drug during its clinical investigation. Moreover, the dose and formulation of drug are chosen so as not to lower the BP too much or too fast, to avoid hypotensive side effects. Virtually all oral drugs are

designed to do the same thing: lower the BP at least 10% in the majority of patients with mild to moderate hypertension (Kaplan, 1992).

Not only must each new drug be shown to be effective in large numbers of hypertensive patients but the drug also must have been tested against currently available agents to show at least equal efficacy. When comparisons between various drugs are made, they almost always come out close to one another. The best such comparison was performed in the TOMHS study (Neaton et al., 1993). The TOMHS study involved random allocation of five drugs (chlorthalidone, acebutolol, doxazosin, amlodipine, and enalapril), each given to almost 200 mild hypertensives, while another group took a placebo and all patients remained on a nutritional-hygienic program. The overall antihypertensive efficacy of the five drugs over 4 years was virtually equal (Neaton et al., 1993).

Despite the fairly equal overall efficacy of various antihypertensive drugs, individual patients may vary considerably in their response to different drugs. Some of this variability can be accounted for by patient characteristics, including age and race. This was seen in a VA cooperative 1-year trial in which 1,292 men were randomly given one of six drugs from each major class: Overall, and in the black patients, the CCB was most effective, but the ACEI was best in younger whites, and the b-blocker was best in older whites (Materson et al., 1993, 1995). Similarly, in a randomized crossover trial of elderly patients with isolated systolic hypertension given a representative of four major classes—ACEI, b-blocker, CCB, and diuretic—each for 1 month, the diuretics and CCB were more effective than the b-blocker or ACEI (Morgan et al., 2001). In a similarly designed trial of younger patients with combined systolic and diastolic hypertension, the ACEI and b-blocker were more effective than the CCB or diuretic (Dickerson et al., 1999).

Individual Trials of Efficacy

Because individual patients do vary in their response, individual patient randomized clinical trials, referred to as “ *n* of 1” (Jaeschke and Guyatt, 1990), have been proposed to ascertain the best drug for each patient. The idea is simple: The patient undergoes successive treatment periods, each providing an active drug and a matched placebo assigned at random, with both the patient and the physician blinded to the choice, which is made by the pharmacist. The process can go on as long as needed until an effective and well-tolerated agent is found for each individual patient, using home BP monitoring (Chatellier et al., 1995).

Although the concept is simple, I doubt whether many practitioners (or their patients) will go to that much trouble. Fortunately, the physician can make a fairly exact ascertainment, if not of the best drug, certainly of an effective and well-tolerated one. This simply requires an open mind, a willingness to try one drug after another (each chosen from the major classes of available antihypertensive agents) with careful monitoring of the patient (preferably by using home BP readings), and a thorough ascertainment of side effects.

Comparisons between Drugs: Reductions in Morbidity and Mortality

The critical issue is not efficacy in lowering BP but rather effectiveness in reducing morbidity and mortality. As detailed in Chapter 5, all major classes of antihypertensive drugs except a-blockers have been shown to reduce mortality and morbidity in large RCTs, and there are few differences between them (Blood Pressure Lowering, 2000; Psaty et al., 1997; Staessen et al., 2001).

In all of the 18 RCTs completed before 1995, diuretics or b-blockers were used (Psaty et al., 1997). In the eight RCTs completed between 1995 and 2000, ACEIs or CCBs were compared either against a diuretic with or without a b-blocker or against one another (Blood Pressure Lowering, 2000). As seen in Table 7-12, one conclusion from these more recent trials seems obvious: Neither ACEI-based nor CCB-based therapies are better than are therapies based on diuretics with or without a b-blocker. CCB therapy did protect better against stroke and less well against CHD and CHF, but ACEIs and CCBs provided identical effects on overall morbidity and mortality (Staessen et al., 2001).

	Relative risks (confidence intervals)					
	Stroke	CHD	CHF	Major CV events	CV death	Total mortality
ACEI vs. D/BB (5 trials; 16,161 pts)	1.05 (0.92–1.19)	1.00 (0.88–1.14)	0.92 (0.77–1.09)	1.00 (0.93–1.08)	1.00 (0.87–1.15)	1.03 (0.93–1.14)
CCB vs. D/BB (5 trials; 23,454 pts)	0.87 (0.77–0.98)	1.12 (1.0–1.26)	1.12 (0.95–1.33)	1.02 (0.95–1.10)	1.05 (0.92–1.2)	1.01 (0.93–1.11)
ACEI vs. CCB (2 trials; 4,671 pts)	1.22 (0.95–1.21)	0.81 (0.58–0.97)	0.82 (0.67–1.0)	0.92 (0.83–1.01)	1.04 (0.87–1.24)	1.03 (0.91–1.18)

ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CCB, calcium channel blocker; CHD, coronary heart disease; CHF, congestive heart failure; CV, cardiovascular; D, diuretic; pts, patients.
Modified from the Blood Pressure Lowering Treatment Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs. Lancet 2000;356:1955–1964.

TABLE 7-12. *Prospective overview of comparative randomized trials for hypertension*

The bottom line of Table 7-12 shows data from the two trials directly comparing an ACEI to a CCB. The Appropriate Blood Pressure Control in Diabetes trial (Schrier and Estacio, 2000) had 470 patients, whereas the Swedish Trial in Old Patients with Hypertension, part 2 (STOP-2) (Hansson et al., 1999) had 4,401 taking either an ACEI or a CCB, so obviously most of the results are derived from STOP-2. Although there is apparently lesser protection against CHD and CHF with the CCB than with the ACEI, the words of the principal investigators of STOP-2 should be heeded: “Our results should be interpreted with some caution, since 48 statistical comparisons were done. Calcium antagonists were not, however, less effective in any other way in the prevention of cardiovascular events than conventional drugs or ACEIs, which accords with current opinion about safety of calcium antagonists when used appropriately” (Hansson et al., 1999).

The results of the eight comparative trials completed since 1995 are by no means definitive. As He and Whelton (2000) note, “Most of the uncertainties related to selection of initial antihypertensive drug therapy will be resolved by trials in progress and by the pooling of the findings from these trials.” Fortunately, a large number of trials are in progress so that before long we should have more definitive data to guide our choices in therapy. These data will include outcome studies with ARBs.

Of course, the playing field keeps growing. By the time we know whether ARBs are as good as ACEIs, vasopeptidase inhibitors will likely be available, so the process of finding out what's best will likely never end.

In one sense, the process is irrelevant. As the need to achieve lower goals of therapy has become obvious, the need to use more than one drug in the majority of hypertensives has also become obvious. This is nowhere better seen than among diabetic hypertensives who will be considered later in this chapter. Therefore, the best combination of agents, almost always to include a low dose of diuretic, will be a more pertinent object of trials in the future.

Comparisons between Drugs: Adverse Effects

As to the issue of differences in adverse effects among different agents, two points are obvious: First, no drug that causes dangerous adverse effects beyond a rare idiosyncratic reaction when given in usual doses will remain on the market, even if it slips by the approval process, as witnessed by the CCB mibefradil. Second, drugs that cause frequent bothersome, although not dangerous, adverse effects, such as guanethidine, will likely no longer be used now that so many other choices are available.

The various antihypertensive agents vary significantly, both in the frequency of adverse effects and, to an even greater degree, in their nature. The only currently available comparisons of a representative drug from all major classes given as monotherapy to sizable numbers of patients are TOMHS (Neaton et al., 1993) and the VA Cooperative Study (Materson et al., 1993, 1995). Side effects differed between the drugs, but no one drug was markedly more or less acceptable than the others. The differences may include sexual dysfunction. Impotence was twice as common in men in the TOMHS study given the diuretic chlorthalidone than in those given a placebo, whereas less impotence was seen among those given the a-blocker doxazosin (Grimm et al., 1997).

Quality of Life

Over the last 25 years, a number of studies have examined the side effects of antihypertensive agents on QOL using various questionnaires and scales (Testa, 2000).

Only nine of those published through 1991 met the criteria of comparing active treatment to baseline measures with the patients as their own controls in blinded, randomized trials, but these involved 1,620 patients in 27 groups using 14 drugs from 6 of the 7 major classes (Beto and Bansal, 1992). Beto and Bansal's (1992) metaanalysis assessed the effects of drugs on five specific QOL measures: sexual function, sleep, psychomotor abilities, mood, and general well being. The overall effect was found in all nine studies to be significantly positive for all measures except for a neutral effect on sexual function and differed little between the six types of drugs.

These results confirm the general impression: Although 10% to 20% of patients will experience bothersome adverse effects from virtually any and every antihypertensive drug, the overall impact of therapies on QOL over 2 to 6 months of observation is positive (Weir et al., 1996; Wiklund et al., 1999). However, different drugs do have different profiles of side effects, and only by careful observations can subtle differences be detected, as with sexual dysfunction in the TOMHS (Grimm et al., 1997).

Apparent Intolerance to All Drugs

Some patients have adverse effects from every drug they take, often bringing to the office a long list of what they have been unable to tolerate. In a few, this may reflect successful reduction in BP below the threshold of cerebral autoregulation by usual doses of drugs so that the patient appears to be intolerant to all medications. Some of these highly susceptible patients can be treated with very small doses of an appropriate agent, because they may be to the far right of the curve of responsiveness.

Much more common is the mistaken attribution of anxiety-related symptoms to the blameless drug. As noted in Chapter 15, anxiety-induced hyperventilation is common in hypertensives whose BP is difficult to control, often exacerbated by the belief that “the silent killer” is soon to strike again. Here again, starting therapy with very small doses of a new drug that has never been taken before, along with behavioral cognitive therapy to relieve the anxiety (and often rebreathing into a paper sack to overcome acute symptoms), may help these difficult patients.

Effects

In addition to these QOL issues, more serious problems have been blamed on various classes of antihypertensive drugs. Virtually all these claims have come from noncontrolled, often retrospective, observational case-control studies, and most of them have been subsequently proved to be wrong (Kizer and Kimmel, 2001).

Cancer from Reserpine, Calcium Channel Blockers, and Diuretics

The first and perhaps most egregious claim was that the use of reserpine was associated with a twofold to fourfold increased risk of breast cancer in women, a claim made in three simultaneously published papers from outstanding investigators (Armstrong et al., 1974; Boston Collaborative, 1974; Heinonen et al., 1974). As subsequently shown by Feinstein (1988), these studies were all contaminated by the bias of excluding women at high risk for cancer from the control groups. Multiple subsequently published prospective studies showed no association (Mayes et al., 1988).

More recently, Pahor et al. (1996a, 1996c) reported a twofold greater risk for cancer in elderly patients taking short-acting CCBs as compared to users of b-blockers. Unfortunately, they made no ascertainment of drug use after the original observation that the subjects had the respective drugs in their possession, so that the actual intake of drugs is totally unknown. Multiple subsequent reports of much larger populations in which drug use was appropriately ascertained have found *no increase* in cancer among users of CCBs. In addition to ten studies published by early 1998 that were reviewed by Mason (1999), at least seven more published since then have found no relationship (Cohen et al., 2000; Lindholm et al., 2001; Meier et al., 2000; Peeters et al., 1998; Sajadieh et al., 1999; Stahl et al., 2000; Vezina et al., 1998). Moreover, in the massive placebo-controlled Syst-Eur trial in the elderly, the incidence of cancer was 31% *less* in those taking the CCB than in those on placebo (Staessen et al., 1997).

On the other hand, there may be an association between diuretic use and cancers arising in renal cells (Grossman et al., 2001) or colon (Tenenbaum et al., 2001). The association with renal cell cancers has been repeatedly observed and could reflect conversion of thiazides to mutagenic nitroso derivatives in the stomach. As noted by Hamet (1996), these claims must all be balanced against the multiple observations that the rates of cancer are increased among untreated hypertensives as well as obese patients (Yuan et al., 1998). Even if the association is true, the incidence is nonetheless so low as to be far overshadowed by the known benefits of diuretic therapy (Lip and Ferner, 1999).

Coronary Disease from Calcium Channel Blockers and b-Blockers

Psaty et al. (1995) reported a 60% increase in the risk of acute MI among patients taking short-acting CCBs. This report coincided with republication of a metaanalysis of the adverse effects of high doses of short-acting CCBs in the immediate post-MI period (Furberg et al., 1995). The two publications received tremendous press coverage claiming that CCBs could endanger more than 6 million hypertensives in the United States alone, leading to major disruptions in the management of patients with both angina and hypertension who were receiving these agents (Lenfant, 1995).

Psaty et al. (1995) and Furberg et al. (1995) strongly suggested that their claims against short-acting CCBs (which had never been approved for the treatment of hypertension) also carried over to the longer-acting agents (which are approved for the treatment of hypertension). As Epstein (1996) and I (Kaplan, 1996a, 1996b) pointed out, there are significant differences in the hemodynamic and hormonal responses to short-acting versus long-acting CCBs, so that the faults of the former should not be assumed to apply to the latter.

On the other hand, three of four cohort observational studies have shown a higher mortality rate among CCB users than users of other drugs (Maxwell et al., 2000; McInnes et al., 2000; Michels et al., 1998). No such increased mortality risk for CCB users was found among the 3,539 subjects in the Framingham Heart Study (Abascal et al., 1998). As Michels et al. (1998) conclude, “Whether the observed elevated risk [in CCB users] is real, or a result of residual confounding by indication, or chance, or a combination of the above cannot be evaluated with certainty on the basis of these observational data.” The probability that confounding was a major factor in these associations is supported by the finding that, among 77,000 patients, the likelihood of being prescribed a CCB rather than other antihypertensives was significantly higher for patients with coexisting coronary disease (7.8-fold) or diabetes (1.5-fold) (Leader et al., 2001).

Prospective, controlled data show no increase in coronary disease among users of long-acting CCBs (Alderman et al., 1997; Gong et al., 1996; Leader et al., 1997; Packer et al., 1996b; Staessen et al., 1997). In the case-control study by Alderman et al. (1997), patients receiving short-acting CCBs were found to have a 3.9-fold increased risk for coronary disease as compared to hypertensives taking a b-blocker, whereas those receiving long-acting CCBs actually had a lesser risk (0.76). In the Syst-Eur RCT of elderly patients with systolic hypertension, less morbidity and mortality from coronary disease were seen in those on the CCB than in those on placebo (Staessen et al., 1997).

As seen in Table 7-12, in the comparative trials in which all patients were treated with active drugs, the increase in coronary events seen with CCBs as compared to other drugs was largely balanced by a lower risk of strokes in the CCB-treated patients, with no differences in mortality between different drug classes (Blood Pressure Lowering, 2000). As previously noted, data from ongoing, large comparative trials will settle the issue once and for all.

Gastrointestinal Bleeding

Pahor et al. (1996b) observed an increase in gastrointestinal bleeding in a cohort study of 1,636 elderly hypertensives. Similar increased risk was reported by these investigators in two other groups (Kaplan et al., 2000; Zuccalá et al., 2000) and by Rodriguez et al. (1998), but no such risk has been noted by others (Desboeuf et al., 1998; Kelly et al., 1999; Smalley et al., 1998; Suissa et al., 1998).

Dose-Response Relationships

Need to Avoid Overdosing

Beyond the individual variabilities in response to drugs, there is a more generalized problem with the use of antihypertensive agents: They often are prescribed in doses that are too high (Kaplan, 1992). The problem of overdosing has been obvious with virtually every new drug introduced, wherein the initial recommended doses

have been gradually reduced because, after widespread clinical experience, they proved to be too high (Johnston, 1994). Whereas 100 to 200 mg HCTZ was initially used, 12.5 mg is now recognized as enough for many patients. The initial recommended daily dose of captopril was up to 600 mg; now 50 to 100 mg is usually prescribed.

The problem arises in the preapproval testing of new drugs, as described by Herxheimer (1991):

> For a new drug to penetrate the market quickly, it should be rapidly effective in a high proportion of patients and simple to use. To achieve this, the dosage of the first prescription is therefore commonly set at about the ED90 level— i.e., the dose which the early clinical (phase II) studies have shown to be effective in 90% of the target population, provided that the unwanted effects at this dose are considered acceptable. In 25% of patients a smaller, perhaps much smaller, dose (the ED25) will be effective. The patients in this quartile are the most sensitive to the drug and are liable to receive far more than they need if they are given the ED90. They are also likely to be more sensitive to the dose-related side effects of the drug.

This may very well be the explanation for the ongoing issue over the first vasopeptidase inhibitor, omapatrilat. The initial trials used a somewhat higher dose in order to achieve greater effectiveness, but this higher starting dose may have led to more frequent occurrences of angioedema (Messerli and Nussberger, 2000).

The obvious solution to this problem is for practitioners to start patients with doses that will not be fully effective and to titrate the dose gradually to the desired response. As Herxheimer (1991) notes:

> The disadvantage from the marketing stand-point is that for the majority of patients the dose must be titrated. That is time-consuming for doctors and patients and more difficult to explain to them. A drug requiring dose titration cannot be presented as the quick fix, the instant good news that marketing departments love.

Need to Lower the Pressure Gradually

The “quick fix” is inappropriate for most patients and, in a large trial with an ACEI, slower dose escalation (every 6 weeks) was shown to provide higher BP control rates and fewer serious adverse events than more rapid escalation (every 2 weeks) (Flack et al., 2000). These results are in keeping with what is known about the autoregulation of cerebral and coronary blood flow (Strandgaard and Haunsø, 1987) supporting the need for a slow and gradual fall in BP to maintain blood flow to vital organs. Normally, CBF remains relatively constant at approximately 50 mL per minute/100 g of brain (Strandgaard and Paulson, 1996). When the systemic BP falls, the vessels dilate; when the BP rises, the vessels constrict. The limits of cerebral autoregulation in normal people are between mean arterial BPs of about 60 and 120 mm Hg (e.g., 80/50 to 160/100 mm Hg).

In hypertensives without neurologic deficits, the CBF is not different from that found in normotensives. This constancy of the CBF reflects a shift in the range of autoregulation to the right to a range of mean BP from approximately 100 to 180 mm Hg (e.g., 130/85 to 240/150). As seen in Figure 7-15, this shift maintains a normal CBF despite the higher BP but makes the hypertensive vulnerable to cerebral ischemia when the BP falls to a level that is well tolerated by normotensives.

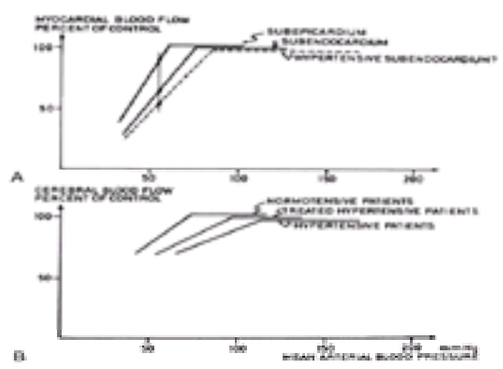


FIG. 7-15. Autoregulation of **(A)** myocardial and **(B)** cerebral blood flow. Mean myocardial blood flow autoregulation curves are shown for subepicardium and corresponding subendocardial layers of the left ventricle in canine hearts. The autoregulatory curve of subendocardial blood flow in hypertensive hearts is suggested. During low arterial pressure (*vertical line*, **A**), when autoregulation is exhausted in both myocardial layers, subendocardial blood flow is lower than in the more superficial layers of the left ventricle. Mean cerebral blood flow autoregulation curves from normotensive, severely hypertensive, and effectively treated hypertensive patients are shown. (Reprinted from Strandgaard S, Haunsø S. Why does antihypertensive treatment prevent stroke but not myocardial infarction? *Lancet* 1987;2:658–661, with permission.)

Note that the lower limit of autoregulation capable of preserving CBF in hypertensive patients shown in Figure 7-15 is at a mean BP of nearly 110 mm Hg. Thus, acutely lowering the BP from 160/100 mm Hg (mean, 127 mm Hg) to 140/85 mm Hg (mean, 102 mm Hg) may induce cerebral hypoperfusion, although hypotension in the usual sense has not been induced. This likely explains why many patients experience manifestations of cerebral hypoperfusion (weakness, easy fatigability, and postural dizziness) at the start of antihypertensive therapy, even though BP levels do not seem inordinately low.

Fortunately, with effective control of the BP by medication, the curve drifts back toward normal, explaining the eventual ability of hypertensive patients to tolerate falls in BP to levels that initially produced symptoms of cerebral ischemia. Not all patients show a readaptation toward normal; presumably their structural changes are not reversible. Thus, older patients with more cerebral atherosclerosis may remain susceptible to cerebral ischemia when their BP is lowered even gently (Somes et al., 1999; Vokó et al., 1999).

The coronary circulation, particularly in those with extensive atherosclerosis, may also autoregulate very poorly, and patients with preexisting coronary artery disease may be particularly prone to subendocardial ischemia as their BP is lowered (Cruickshank, 1988; Strandgaard and Haunsø, 1987). Because the hypertrophied myocardium often found in chronic hypertensives, which requires more oxygen, can extract little beyond what is removed under normal conditions, the vulnerability of patients to myocardial ischemia when their BP is lowered below the critical level needed to maintain adequate perfusion is easily understood (see Chapter 5).

Need for 24-Hour Coverage

As noted in Chapter 2, self-recorded measurements and ambulatory automatic BP monitoring are being increasingly used to ensure the 24-hour duration of action of antihypertensive agents. This is particularly critical with the increasing use of once-a-day medications that often do not provide 24-hour efficacy (Lacourcière et al., 2000). Therefore, the patient is exposed to the full impact of the early morning, abrupt rise in BP that is almost certainly involved in the increased incidence of various cardiovascular events immediately after arising (Munger and Kenney, 2000).

Although ambulatory automatic BP monitoring is not available for most patients, self-recorded measurements with inexpensive semi-automatic devices should be possible for most, thereby ensuring the adequacy of control throughout the waking hours—particularly the early morning hours (Mancia et al., 1998). Caution is advised against having patients take those medications that have their maximal effect within 2 to 4 hours late in the evening or before retiring because, as noted in Chapter 2, the BP usually falls considerably during sleep. Hypotension and tissue ischemia could thereby be induced (Mancia, 1993). A formulation of verapamil has become available that releases the medication only after a 4- to 6-hour interval, so bedtime dosing is appropriate (Smith et al., 2001). For now, if patients awake because of nocturia some 2 or 3 hours before arising for the day, they can be instructed to take their medication at that time.

Value of Greater than 24-Hour Efficacy

Drugs that continue to work beyond 24 hours are even more attractive to prevent loss of control in the considerable number who skip a dose at least once weekly, as documented in 30% or more of patients with hypertension (Rudd, 1995). A small but, hopefully, increasing number of drugs are available that will maintain good efficacy on a missed day (Myers, 2000). These include the CCB amlodipine (Zannad et al., 1999) and the ACEIs perindopril (Tan and Leenen, 1999) and trandolapril (Meredith, 1996). In the study shown in Figure 7-16, once-daily enalapril did not have sustained efficacy in the initial 24 hours and provided almost no effect in the second 24 hours, whereas trandolapril maintained full efficacy throughout the day of intake and most of its effect on the next day as well, when no drug was taken.

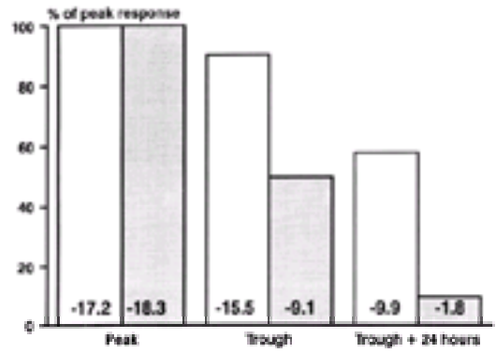


FIG. 7-16. Systolic blood pressure responses to enalapril (shaded bars) and trandolapril (open bars) at steady state and 24 hours after a missed dose. (Reprinted from Meredith PA. Implications of the links between hypertension and myocardial infarction for choice of drug therapy in patients with hypertension. Am Heart J 1996;132:222–228, with permission.)

CHOICE OF DRUGS: FIRST, SECOND, AND BEYOND

Now that the effectiveness and safety of various antihypertensive agents have been compared and important pharmacologic considerations have been emphasized, we will turn to the practical issue of which of the many drugs now available (Table 7-13) should be the first, second, or subsequent choices in individual patients. As noted previously and shown in Figure 7-1, major changes in these choices have occurred.

TABLE 7-13. *Oral antihypertensive drugs available in the United States*

Before proceeding into the specifics, we need to recall the overriding issue: to lower the BP to reduce cardiovascular risk maximally without decreasing (and perhaps even improving) the enjoyment of life. The preferred qualities of the drugs are fairly obvious, but none now available (or likely to become available) meets all the criteria for perfection. Nonetheless, currently available choices come close and, used adroitly, can protect almost all patients without much bother.

One impediment is threatening to interfere with clinicians' ability to use the therapy of their choice: restrictive formularies that often provide only the least expensive drugs even if they are not the most appropriate for patients' needs (Stein et al., 1997). Moreover, with a plethora of health care organizations, multiple formularies may compound the problems, irritating physicians who must receive authorization before using a nonformulary drug and confusing patients with frequent switches in their medication. Care must be taken to ensure that formularies provide long-acting, once-a-day preparations of at least one member of each major class of antihypertensive, thereby allowing improvement of patient care and reduction of costs.

Choice of First Drug

As more patients with milder hypertension are being treated with drugs, the choices of therapy, particularly for the first drug, should be made with care. The first drug chosen may be taken for 10, 20, 30, or 40 years. Therefore, adverse effects that may not be obvious must be considered. The issue was portrayed in a review of the impact of predominantly diuretic and b-blocker therapies on the BP and other risk factors in 281 patients treated in a major Australian hypertension center (Jennings and Sudhir, 1990). Although hypertension was well controlled, renal function, blood glucose, and cholesterol levels worsened. As summarized in Table 7-13, all drugs may have adverse effects, and precautions are needed in the use of any and all.

Comparative Trials

As reviewed in Chapter 5, RCTs have compared the long-term ability of four classes of antihypertensive drugs—diuretics, b-blockers, ACEIs, and CCBs—to protect patients from overall and cardiovascular morbidity and mortality, the only meaningful criterion. Multiple trials, most comparing two or more drugs against one another, are in progress. Until the results of such trials become available, those who believe that clinical decisions must be evidence-based argue that those drugs that have been tested and found to reduce cardiovascular morbidity and mortality should be chosen (Spector and Vesell, 2000).

Expert Committee Recommendations

This is the position taken in the JNC-6 (Joint National Committee, 1997), as seen in Figure 7-17:

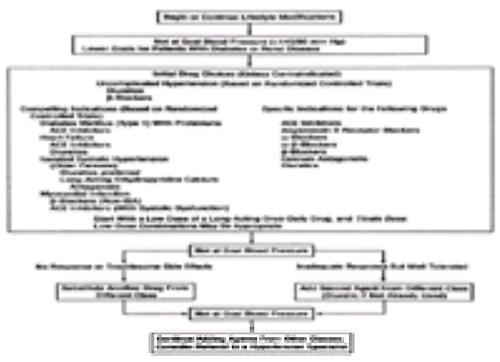


FIG. 7-17. Simplified algorithm for treatment of hypertension. ACE, angiotensin-converting enzyme; ISA, intrinsic sympathomimetic activity. [Reprinted from Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 1997;157: 2413–2446, with permission.]

If there are no specific indications for another type of drug, a diuretic or beta-blocker should be chosen because numerous RCTs have shown a reduction in morbidity and mortality with

these agents. In the elderly, diuretics should be chosen. Only one RCT has studied the use of a long-acting dihydropyridine calcium antagonist (nitrendipine) in elderly patients with isolated systolic hypertension [Staessen et al., 1997]. The trial demonstrated a 42-percent reduction in stroke mortality. There was not a statistically significant decrease in coronary events, although a downward trend was reported. Although nitrendipine is not currently available in the United States, long-acting dihydropyridine calcium antagonists may be considered for initial ther apy in the elderly. If specific indications for other agents are present, the choice should be individualized, using the agent that most closely fits the patient's need [Table 7-14].

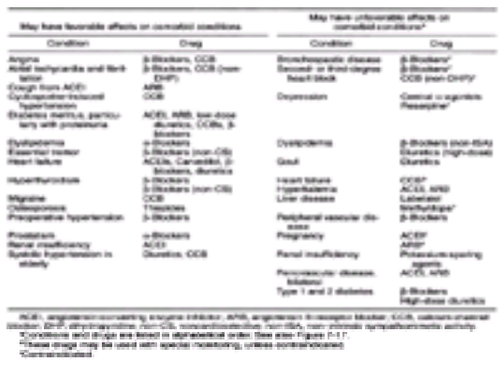


TABLE 7-14. *Considerations for individualizing antihypertensive drug therapy*[a]

In 1999, additional guidelines composed by expert committees worldwide (Guidelines Sub-committee, 1999), in the United Kingdom (Ramsay et al., 1999), and in Canada (Feldman et al., 1999) have, with comforting uniformity, agreed with the JNC-6 position, while adding additional “compelling” and “favorable” indications for specific drugs on the basis of newly available evidence.

As of 2001, there remains no conclusive evidence for the superiority of one or another class of drugs in the overall hypertensive population (He and Whelton, 2000; MacMahon and Neal, 2000). As these editorialists note, “Most of the uncertainties related to selection of initial drug therapy will be resolved by trials in progress and by the pooling of the findings from these trials” The JNC-6 (Joint National Committee, 1997)

Once-Daily Therapy

The JNC-6 (Joint National Committee, 1997) states:

> For most patients, a low dose of the initial drug choice should be used, slowly titrating upward at a schedule dependent on the patient's age, needs, and responses. The optimal formulation should provide 24-hour efficacy with a once-daily dose, with at least 50 percent of the peak effect remaining at the end of the 24 hours. Long-acting formulations that provide 24-hour efficacy are preferred over short-acting agents for many reasons: (1) adherence is better with once-daily dosing; (2) for some agents, fewer tablets incur lower cost; (3) control of hypertension is persistent and smooth rather than intermittent; and (4) protection is provided against whatever risk of sudden death, heart attack, and stroke that is due to the abrupt rise of blood pressure after arising from overnight sleep. Agents with a duration of action beyond 24 hours are attractive because many patients inadvertently miss at least one dose of medication each week.

Recall the value of home BP measurements, particularly in the early morning before patients take their daily dose, to ensure that they are obtaining enough of a sustained effect to blunt the early morning surge in BP after arising. If the response to a new therapy is being monitored, repeated BPs throughout the day will be helpful in determining the degree of response, particularly to avoid overtreatment of the elderly.

Other Considerations

JNC-6 subsequently details a number of other factors to be considered in the selection of drugs, including “demographic characteristics, concomitant diseases that may be beneficially or adversely affected by the antihypertensive agent chosen, quality of life, cost, and the use of other drugs that may lead to drug interactions” (Joint National Committee, 1997). These additional factors will translate into a continuation of current trends—the use of various classes, with the specific drug chosen on the basis of multiple considerations, an approach best described as *individualized*.

Individualized Therapy

The individualized approach is predicated on three major principles:

- The first choice may be one of a variety of anti-hypertensives from any of the major classes of drugs.
- The choice can be logically based on the characteristics of the patients, in particular, the presence of concomitant diseases.
- Rather than proceeding with a second drug if the first is not effective or if side effects ensue, a substitution approach is used; stop the first drug and try another from a different class.

Let us consider further these three principles.

Characteristics of the Drugs

Each class of drugs has different features that make its members more or less attractive, as summarized in Table 7-15.

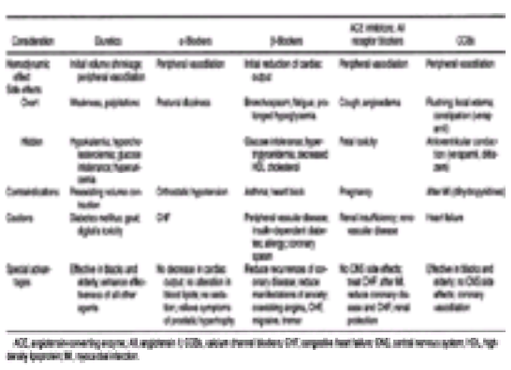


TABLE 7-15. *Characteristics of major classes of antihypertensive drugs*

Diuretics

In the past, diuretics were almost always chosen first, because they were considered free of significant side effects, easy to take, and inexpensive. Moreover, reactive fluid retention with other drugs used without a diuretic often blunted their effect, so the idea of using a diuretic first seemed logical. However, recognition of the “hidden” side effects and costs of diuretics, along with the lesser protection from coronary mortality in the initial trials wherein they were used in high doses, caused many investigators to doubt the wisdom of routine use of diuretics. At the least, these factors have led to the more widespread use of lower doses of diuretics and their combinations with potassium-sparing agents. However, as shown in Chapter 5, diuretic-based therapy is clearly protective and, as noted earlier in this chapter,

has now been shown to be as protective as either ACEI- or CCB-based therapies.

b-Blockers

In the 1970s and 1980s, b-blockers became increasingly popular. However, contraindications to their use and recognition of their potential for altering lipids adversely dampened their popularity. The failure to find primary protection against coronary disease in trials with a b-blocker, as described in Chapter 5, further weakened the argument for their use. However, their ability to provide secondary cardioprotection and to treat heart failure has recently embellished their status.

Indirect Vasodilators

Drugs that act primarily as indirect vasodilators—a-blockers, ACEIs, and CCBs—are being more widely advocated for initial therapy. There seems to be an inherent logic in using drugs that induce vasodilation, as an elevated peripheral resistance is the hemodynamic fault of established hypertension. Their relative benefits in various situations have been covered earlier, as has the issue of possible dangers from CCBs.

Other Agents

Reserpine works as well as any of these drugs with one dose per day, but it is no longer being advertised and is little used. As to the use of the other classes of drugs for initial therapy, JNC-6 (Joint National Committee, 1997) states:

> Some antihypertensive agents—such as the direct-acting smooth-muscle vasodilators, central alpha2-agonists, and peripheral-acting adrenergic antagonists—are not well suited for initial monotherapy because they produce annoying adverse effects in a large number of patients. . . . The direct-acting, smooth-muscle vasodilators (e.g., hydralazine, minoxidil) often induce reflex sympathetic stimulation of the cardiovascular system and fluid retention.

Characteristics of the Patient

Demographic Features

Individual patient's characteristics may affect the likelihood of a good response to various classes of drugs. As shown in crossover rotations of the four major classes (Dickerson et al., 1999; Morgan et al., 2001), younger, white patients will usually respond better to either an ACEI or a b-blocker, perhaps because they tend to have higher renin levels, whereas older and black patients will respond better to diuretics and CCBs, perhaps because they have lower renin levels and their hypertension is more “volume-mediated” (Laragh, 2001). These differences apply to monotherapy; with a low-dose of a diuretic as part of the regimen, responses to all other agents are largely equalized. Moreover, for the individual patient, any drug may work well or poorly, and there is no set formula that can be used to predict certain success without side effects.

The individual patient comparative trial described earlier in this chapter could be used to determine which is the best choice. Practically, if the patient's BP is well controlled and no bothersome or potentially hazardous adverse effects are present, there is no reason to keep searching for the best. Rather than searching for perfection, we need simply to weed out the drugs that either produce little good effect or induce significant ill effects.

Concomitant Conditions

Patients with hypertension, particularly the elderly, often have other medical problems, some related to their hypertension, others coincidental. As shown in Table 7-14, a hypertensive patient with angina would logically be given a b-blocker or a CCB, a patient with CHF, an ACEI and diuretic. a-Blockers, CCBs, and ACEIs are attractive choices for those in whom a diuretic or b-blocker may pose particular problems, such as diabetics or hyperlipidemic patients. In an elderly hypertensive man with benign prostatic hypertrophy, an a-blocker would be a logical choice. In view of the benefits of addition of the ACEI ramipril to the therapy of high-risk patients shown in the HOPE trial, the principal investigator of that trial has stated that “it would be appropriate to use ramipril in all suitable patients at high risk for atherothrombotic cardiovascular events” (Yusuf, 2001). In lower-risk patients, there is less enthusiasm for ACEIs (Fournier et al., 2001). These authors note that the diabetic patients without cardiovascular disease in the HOPE trial did not have a significant decrease in primary outcomes with ramipril (Heart Outcomes Prevention Evaluation, 2000b) and that a case-control study of lower-risk hypertensives found a 2.8-fold lower risk of stroke in those given a diuretic as compared to those given an ACEI (Klungel et al., 2000).

Plasma Renin Levels

Laragh and co-workers, as far back as 1972 (Bühler et al., 1972), have used the level of PRA to guide the choice of initial therapy. As attractive as the concept is, in practice it often does not work: Donnelley et al. (1992) found that pretreatment PRA accounted for considerably less than 10% of the variability in response to treatment. Nonetheless, use of age and race as a proxy for PRA levels is useful: The elderly and blacks may respond particularly well to diuretics because their renin levels tend to be lower, whereas younger and white patients may respond well to b-blockers or ACEIs because their renin levels are higher (Laragh, 2001).

Substitution Rather than Addition

If the first choice, even if based on all reasonable criteria, does not lower the BP much or is associated with persistent, bothersome side effects, that drug should be stopped and one from another class should be tried. Thereby, the least number of drugs should be needed to achieve the desired fall in BP with the fewest side effects.

Patients with milder hypertension will often need only one drug. Therefore, substitution should work for them. For those with more severe hypertension, the first drug may do all that it can and still not be enough. Therefore, the addition of a second or, if needed, a third drug added in a stepwise manner is logical (Fig. 7-17).

High-Risk Patients

JNC-6 (Joint National Committee, 1997) notes that modifications may be needed for those at higher risk of a coronary event or stroke because of other risk factors or target organ damage:

> Although some patients may respond adequately to a single drug, it is often necessary to add a second or third agent after a short interval if control is not achieved. The intervals between changes in the regimen should be decreased, and the maximum dose of some drugs may be increased. In some patients, it may be necessary to start treatment with more than one agent. Patients with average diastolic blood pressure of 120 mm Hg or greater and systolic blood of pressure of 200 mm Hg or greater require more immediate therapy and, if symptomatic target organ damage is present, may require hospitalization.

Cost as a Factor

For some patients, the cost of the medications used to treat hypertension may pose an obstacle to control of their disease, particularly in developing countries (Calvo-Vargas et al., 1998) and in the elderly who are not well insured (Blustein, 2000). The cost per tablet varies between a few cents for a generic HCTZ or reserpine to a dollar or more for a brand name ACEI or CCB. Practitioners concerned about the cost might then choose the least expensive agent.

However, there are additional factors that need to be considered. First, the cost of the tablet may not be the major cost of prescribing the medication (Hilleman et al., 1993). If a diuretic causes hypokalemia that must be corrected, potassium supplements may cost a dollar a day or more. b-Blocker-induced hyperlipidemia that requires an antilipidemic agent is another example.

Second, more and more agents are available in long-acting formulations so that one tablet a day may provide full coverage. The cost may be reduced further by prescribing larger doses of tablets that can easily be cut in half. Although a dollar or more a day may pose a burden for many, the cost of medication should not interfere with the provision of what is best for most patients. Nonetheless, the temptation to go with the least expensive agent cannot be discounted (Johannesson, 1994), particularly because the inexpensive agents have been tested and shown to reduce mortality as well as more expensive agents (Blood Pressure Lowering,

2000).

Follow-Up Visits

Achieving and maintaining target BP with the lowest possible dosage of medication requires ongoing patient follow-up and may involve multiple dosage adjustments. Most patients should be seen within 1 to 2 months after the initiation of therapy to determine the adequacy of BP control, the degree of patient cooperation in taking pills, and the presence of adverse effects. Associated medical problems—including target organ damage, other major risk factors, and laboratory test abnormalities—also play a part in determining the frequency of patient follow-up. Once the BP is stabilized, follow-up at 3- to 6-month intervals (depending on the patient's status) is generally appropriate. In most patients, particularly the elderly and patients with orthostatic symptoms, monitoring should include BP measurement in the supine position and after standing for up to 5 minutes, to recognize postural hypotension.

Choice of Second Drug

If a moderate dose of the first choice is well tolerated and effective but not enough to bring the BP down to the desired level, a second drug can be added, and thereby better control will likely be achieved than by increasing the dose of the first drug (Elliott et al., 1999).

As noted by the Joint National Committee (1997):

> Combinations of low doses of two agents from different classes have been shown to provide additional antihypertensive efficacy, thereby minimizing the likelihood of dose-dependent side effects. Very low doses of a diuretic (e.g., 6.25 mg HCTZ) can potentiate the effect of the other agent without producing adverse metabolic effects (Frishman et al., 1994). Low-dose combinations with an ACEI and a nondihydropyridine calcium antagonist may reduce proteinuria more than either drug alone (Epstein and Bakris, 1996). Combinations of a dihydropyridine calcium antagonist and an ACEI induce less pedal edema than does the calcium antagonist alone (Gradman et al., 1997). In some instances, drugs with similar modes of action may provide additive effects, such as metolazone and a loop diuretic in renal failure.

The large number of recently marketed combination tablets listed in Table 7-16 attests to the attraction of the concept (Hilleman et al., 1999). The majority of combinations logically include a low dose of diuretic (i.e., 6.25–12.5 mg HCTZ or 0.625 mg indapamide) (MG Myers et al., 2000), which will enhance the efficacy of all other agents while inducing minimal or no metabolic mischief (Neutel et al., 1996). In some patients, such as diabetics with nephropathy, a combination of an ACEI and a CCB may turn out to be better than either alone (Taylor and Sunthornyothin, 1999). This combination will reduce the frequency of pedal edema from CCBs (Pedrinelli et al., 2000).

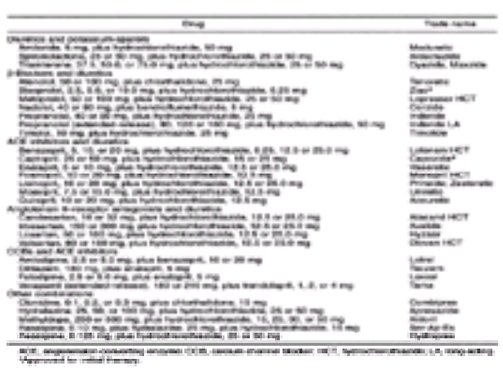


TABLE 7-16. *Combination drugs for hypertension*

Choice of Third or Fourth Drug

Various combinations usually work. In one parallel study, 93 patients uncontrolled on a diuretic and a b-blocker were randomly allocated to nifedipine, prazosin, or hydralazine (Ramsay et al., 1987). After 6 months, all three drugs lowered BPs significantly, and there were few differences among the three groups other than in the pattern of side effects. In a similar study, captopril, nifedipine, and hydralazine were equally effective when added to a diuretic and b-blocker, but the ACEI was better tolerated (Bevan et al., 1993). The key, as with two drugs, is to combine agents with different mechanisms of action.

Few patients should need more than three drugs, particularly if the various reasons for resistance to therapy are considered. For those who do, the JNC-6 (Joint National Committee, 1997) recommends considering referral to a hypertension specialist (Fig. 7-17).

Resistant Hypertension

The reasons for a poor response are numerous (Table 7-17); the most likely is volume overload caused by either excessive sodium intake or inadequate diuretic (Graves, 2000). In one series of 91 patients whose BPs remained above 140/90 mm Hg despite use of three antihypertensive agents, the mechanisms were a suboptimal drug regimen (mainly inadequate diuretic) in 43%, intolerance to medications in 22%, noncompliance in 10%, and secondary hypertension in 11% (Yakovlevitch and Black, 1991). Patients who are hostile (Rutledge et al., 1999) and diabetics (Brown et al., 2000) tend to be more resistant. In a disadvantaged minority population, uncontrolled hypertension is most closely related to limited access to care, noncompliance with therapy, and alcohol-related problems (Shea et al., 1992).

TABLE 7-17. *Causes of inadequate responsiveness to therapy*

Before starting workup for identifiable causes and altering drug therapy, BPs should be checked out of the office setting, because as many as half of resistant patients turn out to have controlled hypertension (Redon et al., 1998). Recall as well the evidence reviewed earlier in this chapter that patients may appear to be resistant only because their physicians simply do not keep increasing their therapy (Berlowitz et al., 1998).

For most resistant patients, in addition to adequate diuretics, therapy should include an ACEI and a CCB, with minoxidil reserved for those who remain resistant (Pontremoli et al., 1991).

Drug Interactions

As shown in Table 7-18, some drug interactions may be helpful; for example, cyclosporine doses can be reduced by verapamil or diltiazem (Abernethy and Flockhart, 2000). Other interactions increase effectiveness of antihypertensive drugs: For example, grapefruit juice and Seville orange juice can inhibit the metabolism of some dihydropyridines such as felodipine by cytochrome P450 enzymes, resulting in significant increases in plasma level of drug (Bailey et al., 2000; Malhotra et al., 2001). Some interactions decrease effectiveness; for example, NSAIDs—including the COX-1-sparing agents (White et al., 2001)—may blunt the actions of diuretics, b-blockers, ACEIs, and ARBs (Conlin et al., 2000a). Of these, celecoxib (Celebrex) causes less interference than rofecoxib (Vioxx) (Whelton et al., 2001).

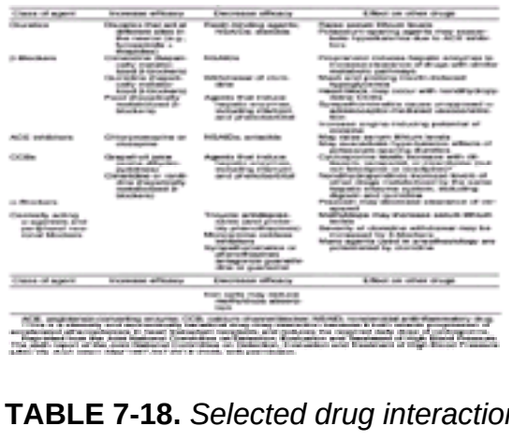


TABLE 7-18. *Selected drug interactions with antihypertensive therapy*

Reduction or Discontinuation of Therapy

Once a good response has occurred and has been maintained for a year or longer, medications may be reduced or discontinued. In a review of all published series of planned withdrawal, 42% of selected patients with mild hypertension were found to remain normotensive for 12 months or longer off medication (Nelson et al., 2001). The characteristics that make withdrawal more likely to be successful were lower levels of BP before and after therapy; fewer and lower doses of medication needed to control hypertension; and patient's willingness to follow lifestyle modifications.

One of the trials included in this review was the Trial of Nonpharmacologic Interventions in the Elderly, in which 886 elderly patients with BP of less than 145/85 mm Hg on one medication went through a two-step attempt at withdrawal of their therapy (Kostis et al., 1998). In the 774 who were successfully withdrawn, the BP remained below 150/90 mm Hg in almost half of those who followed a regimen of weight loss and lower sodium intake over the next 36 months. Only 16% of those who simply stopped their medication without lifestyle modifications remained at less than 150/90 mm Hg (see Fig. 6-1, Chapter 6). No increase in cardiovascular events was seen among those who were able to withdraw from medication and remained normotensive.

Whether it is worth the trouble to stop successful drug therapy completely is questionable. The more sensible approach in well-controlled patients would be first to decrease the dose of whatever is being used (González-Juanatey et al., 1999). If this succeeds, withdrawal may be attempted with continued surveillance of the BP.

SPECIAL CONSIDERATIONS IN THE CHOICE OF THERAPY

Children are covered in Chapter 16; women who are pregnant or on hormones are covered in Chapter 11.

Women

Although women have been thought to derive less benefit than men from antihypertensive therapy (Kaplan, 1995), the analysis by Gueyffier et al. (1997) portrays the situation correctly: Because they start with less risk for cardiovascular disease, they derive less relative benefit from therapy but, in absolute terms, their response is identical to that of men. Women likely respond similarly to various therapies as well.

Blacks and Other Ethnic Groups

As noted in Chapter 4, black hypertensives have many distinguishing characteristics, some which affect their responses to antihypertensive therapy (Gibbs et al., 1999). Poverty and obesity are more prevalent among black hypertensives; both of these conditions may impede the control of hypertension (Blendon et al., 1995). When given equal access to the same treatment, blacks respond as whites do and experience an even lower incidence of cardiovascular disease than do whites (Ooi et al., 1989). However, they may continue to experience a loss of renal function despite apparently good control of hypertension (Walker et al., 1992).

Blacks respond somewhat less well to monotherapy with b-blockers and ACEIs, perhaps because they tend to have lower renin levels, and equally as well to diuretics, CCBs, and a-blockers (Jamerson and DeQuattro, 1996). Those blacks living in the “stroke belt,” the southeastern part of the United States, respond even less well to an ACEI (captopril) or a central a-agonist (clonidine) than do blacks living else-where (Cushman et al., 2000). They respond equally well to a CCB, regardless of residence (Hall et al., 1998; Sareli et al., 2001). Most find diuretics to be an appropriate initial therapy (Gibbs et al., 1999). To achieve adequate control, a diuretic is more often required by blacks than by whites (Materson et al., 1995). Blacks should not be denied b-blockers or ACEIs if special indications for their use are present.

There is no good evidence that Hispanics, Asians, or other ethnic groups differ from whites in their responses to various antihypertensive agents. As noted, both blacks and Asians have a higher incidence of ACEI-induced cough.

Elderly Patients

The majority of people over age 65 have hypertension; in most, the hypertension is predominantly or purely systolic from arterial stiffness. As described in Chapter 4, the risks for such patients are significant. As detailed in Chapter 5, the benefits of treating hypertension in the elderly have been well documented. Now that such evidence is available, many more elderly hypertensives should be brought into active therapy with assurance that debilitating morbidities will be prevented (Staessen et al., 2000), likely including dementia (Birkenhäger et al., 2001). At present, only a small minority of elderly patients with systolic hypertension are being adequately treated (Prisant and Moser, 2000).

Recall the evidence described in Chapter 2 showing that white-coat hypertension is even more common in the elderly than in younger patients (Kaplan, 2000). Therefore, before making the diagnosis, out-of-the-office readings should be obtained, if possible.

Regardless of age, as long as the patient appears to have a reasonable life expectancy, active therapy is likely appropriate for all who have a systolic level above 160 mm Hg, with or without an elevated diastolic pressure. Those at high risk (e.g., diabetics or smokers) should be started on therapy at even lower levels, probably above 140 mm Hg systolic pressure.

Table 7-19 lists factors often present in the elderly that may complicate their therapy. Because the elderly may have sluggish baroreceptor and sympathetic nervous responsiveness, as well as impaired cerebral autoregulation, therapy should be gentle and gradual, avoiding drugs that are likely to cause postural hypotension. Even more caution is advised with the very elderly. Nonetheless, with careful therapy, benefits likely outweigh risks even in the very elderly (Forette et al., 2000).

Factors	Potential complications
Diminished baroreceptor activity	Orthostatic hypotension
Impaired cerebral autoregulation	Cerebral ischemia with small falls in systolic pressure
Decreased intravascular volume	Orthostatic hypotension Volume depletion, hyponatremia
Sensitivity to hypokalemia	Arrhythmia, muscular weakness
Decreased renal and hepatic function	Drug accumulation
Polypharmacy	Drug interaction
Central nervous system changes	Depression, confusion

TABLE 7-19. *Factors that might contribute to complications from pharmacologic treatment of hypertension in the elderly*

Lifestyle Modifications

Before we rush into drug therapy, the multiple benefits of nondrug therapies that were described in Chapter 6 need to be reaffirmed. The ability of lifestyle changes to lower BP in the elderly has been well documented (Moore et al., 2001; Whelton et al., 1998). In particular, dietary sodium should be moderately restricted down to 100 to 120 mmol per day, because the pressor effect of sodium excess and the antihypertensive efficacy of sodium restriction progressively increase with age (Geleijnse et al., 1994) However, the elderly may have at least two additional hurdles to overcome in achieving this goal: First, their taste sensitivity may be lessened, so they may ingest more sodium to compensate; and second, they may depend more on processed, prepackaged foods that are high in sodium rather than fresh foods that are low in sodium.

Drug Treatment

If lifestyle changes are not enough, drug therapy should be started following the principles listed in Table 7-20. Some of these deserve additional comment.

Check for postural and postprandial hypotension before starting.
Choose drugs that will help other concomitant conditions.
For uncomplicated patients, use a thiazide diuretic + potassium sparer.
If a second agent is needed, use a calcium channel blocker.
β-Blockers are not appropriate unless an indication is present (e.g., coronary disease).
Start with small doses, titrating gradually.
Use longer-acting, once-daily formulations.
Avoid drug interactions, particularly from over-the-counter medications (e.g., nonsteroidal antiinflammatory drugs).
Look for subtle, drug-induced adverse effects (e.g., weakness, dizziness, depression, confusion).
Monitor home blood pressures to avoid over- and undertreatment.
Aim for the goal of systolic blood pressure of 140–145 and diastolic blood pressure of 80–85 mm Hg.

TABLE 7-20. *Guidelines in treating hypertension in the elderly*

Postural Hypotension

As noted in Chapter 4, many elderly patients with systolic hypertension have postural (Harrington et al., 2000) and postprandial (Puisieux et al., 2000) hypotension that may require management before the hypertension is addressed. Postural hypotension is even more common in diabetics (Wu et al., 1999) and serves as a marker for the risk of stroke (Eigenbrodt et al., 2000). A succinct summary of the exacerbating factors, pathophysiology, and therapy for postural hypotension is shown in Figure 7-18 (Tonkin, 1995). A few additional points deserve emphasis:

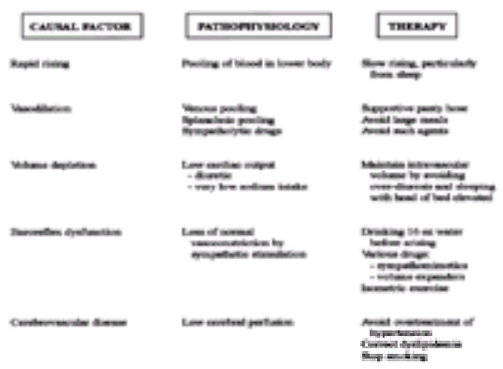


FIG. 7-18. Summary of the pathophysiologic events that occur during the development of symptoms of postural hypertension (middle column) and the interaction of exacerbating factors (left column) and remedial measures (right column) with these events.

- If there are suggestive symptoms (e.g., postural dizziness or unexplained falls), repeated measurements of standing BP may be needed for longer than 2 minutes (Belmin et al., 2000).
- A trial of withdrawal of antihypertensive therapy may be worthwhile if simple measures are not effective (Fotherby et al., 1994); however, postural hypotension may improve after effective antihypertensive therapy (James et al., 1999; Slavachevsky et al., 2000).
- Simple physical countermeasures often do work, including sleeping with the head tilted up (Ten Harkel et al., 1992) and any isometric exercise, but particularly leg crossing and thigh contraction (Bouvette et al., 1996).
- Drinking two full, 8-oz glasses of water before arising may help, likely by an increase in sympathetic activity from rapid distension of the stomach (Jordan et al., 1999).
- Drugs that may work include the partial bagonist pindolol (Mehlsen et al., 1993); erythropoietin (Hoeldtke and Streeten, 1993); the somatostatin analog octreotide [particularly to prevent splanchnic pooling after eating (Jansen and Lipsitz, 1995)]; and the a-agonist midodrine, for those with neurogenic causes (Low et al., 1997).

Choice of Drugs for the Elderly

The initial choice of drug therapy for elderly with LSH now recommended in all the expert guidelines is low-dose diuretics or dihydropyridine CCBs. These recommendations are based on the cardiovascular protection found in the RCTs in which these drugs were used (Staessen et al., 2000). In older patients with combined systolic and diastolic hypertension, therapy based on an ACEI has been shown to be as good, if not better, than that based on diuretics or CCBs (Hansson et al., 1999). Whether this applies to isolated systolic hypertension patients is unknown.

Therapy should begin with small doses and then should be slowly increased: Start low and go slow. Small doses may be fully effective (van de Ven, 1997).

Even more so than in younger patients, the elderly do better with long-acting (once-daily), smoothly working agents; they may have trouble following complicated dosage schedules, reading the labels, and opening bottles with safety caps. Fortunately, when therapy is carefully provided, no loss of cognitive function is seen and dementia may be prevented, as seen in the Syst-Eur trial with the CCB nitrendipine (Forette et al., 1998).

Watch out for drug interactions; the elderly often take multiple medications, some of which (e.g., NSAIDs) interact with many antihypertensive drugs (Barat et al., 2000).

Monitoring of Therapy

Home BP recording may be particularly useful, first in overcoming the white-coat effect, which is quantitatively greater in the elderly and, second, in ensuring that therapy is enough but not too much. The white-coat effect may obscure considerable overtreatment.

Goal of Therapy

As I have written elsewhere (Kaplan, 2000):

> The question of how much should blood pressure be lowered is perhaps the most disturbing in view of evidence that serious consequences are seen with low diastolic blood pressures. These low pressures may occur naturally, as part of the atherosclerotic process (Staessen et al., 2000), or as part of antihypertensive therapy. In the Rotterdam Study involving 2,351 elderly hypertensives, the risk of stroke was significantly higher in those given antihypertensive drugs whose diastolic blood pressure was <65 mm Hg compared with those who had a diastolic pressure between 65 and 74 mm Hg (Vokó et al., 1999). In the recent reanalysis of data from the SHEP, those who experienced a cardiovascular event while on antihypertensive drug therapy had lower diastolic levels than those who did not have an event (Somes et al., 1999). Overall, a further decrease of 5 mm Hg in a diastolic blood pressure (which initially averaged 77 mm Hg) among those who were treated resulted in statistically significant 11% to 14% increases in stroke and cardiovascular events.

Thus there may very well be a J-curve of increasing cardiovascular disease when the diastolic pressure is lowered below the level needed to maintain perfusion to vital organs. . . . Therefore, caution is advised in treating those with [isolated systolic hypertension], who obviously start with already low diastolic blood pressures.

Drugs for the Future

Very limited data suggest that oral nitrate therapy may slow the augmentation of the pulse wave that is largely responsible for the high systolic BPs in the elderly (Stokes et al., 1999; van Bortel et al., 1999). The pulse wave would thereby have less effect on the diastolic BP or, if the augmentation was high enough, it could even cause the diastolic BP to rise (Starmans-Kool et al., 1998). Other agents may be on their way: Preliminary studies found improved arterial compliance with a novel advanced glycation end-product crosslink breaker (Kass et al., 2001).

Hypertensive Patients with Cardiac Disease

Coronary Disease

The presence of angina favors the use of b-blockers (Heidenreich et al., 1999). A CCB and nitrates may also be needed and, on the basis of the HOPE trial, an ACEI will likely be given to most patients with or without hypertension. Hypertension that persists after an acute MI can logically be treated with an ACEI, a non–ISA b-blocker, and a diuretic added if needed.

Congestive Heart Failure

CHF is now classified as secondary either to left ventricular systolic dysfunction (i.e., an ejection fraction less than 40%) or to left ventricular diastolic dysfunction with increased filling pressure and a normal or even high ejection fraction. In systolic dysfunction, because neurohormonal activation as an attempt to maintain tissue perfusion plays such an important role, the value of ACEIs, other vasodilators, and b-blockers has been recognized (Gomberg-Maitland et al., 2001). A diuretic is given if there is evidence of fluid retention and spironolactone in class III to IV CHF. An ARB may be substituted if the patient is intolerant of an ACEI (Pitt et al., 2000b).

There are no large outcome trials for diastolic dysfunction. Therapy is generally similar to that for systolic CHF, with cautions to avoid excessive diuresis and tachycardia (Cody, 2000).

If a CCB is indicated, amlodipine (Packer, 1996b; Pitt et al., 2000a) or felodipine (Cohn et al., 1997) may be used, although no CCB has been shown to have a mortality benefit in CHF (Gomberg-Maitland et al., 2001).

Left Ventricular Hypertrophy

As noted in Chapter 4, LVH is frequently present on echocardiography, even in patients with mild hypertension, and is a major independent risk factor for cardiovascular mortality. Most antihypertensive drugs have been shown to reverse LVH, ACEIs and CCBs somewhat better than diuretics and b-blockers (van Zweiten, 2000). Increasing evidence suggests that such reversal may be helpful (Schussheim et al., 2001; Verdecchia et al., 1998), but it is not certain that the benefit goes beyond that obtained by reduction of BP.

Patients with Cerebrovascular, Peripheral Vascular, or Renal Disease

Cerebrovascular Disease

As detailed in Chapter 8, caution is advised in lowering BP in acute ischemic stroke. However, if brain edema develops, moderate BP reduction aids recovery (Chamorro et al., 1998). CCBs have not been found to reduce mortality or dependency when used within 14 days of stroke (Horn and Limburg, 1999).

After recovery, any persistent hypertension should be vigorously addressed. The control of hypertension has been unequivocally shown to reduce the incidence of stroke (Blood Pressure Lowering, 2000) and is recommended for prevention of stroke recurrence (Wolf et al., 1999). Caution is needed to avoid precipitous falls in BP and to avoid lowering diastolic levels below 65 mm Hg (Vokó et al., 1999). Because ACEIs may preserve CBF better than some other agents, they may be preferred drugs for post-stroke patients (Walters et al., 2001) and, in combination with the diuretic indapamide, the ACEI perindopril reduced recurrences by 43% (PROGRESS Collaborative Group, 2001).

Peripheral Vascular Disease

Because ACEIs (or, if not tolerated, ARBs) and CCBs have been shown to normalize endothelial dysfunction and vascular remodeling in arteries from hypertensive patients (Park and Schiffrin, 2000), they are the logical choices in patients with concomitant peripheral vascular disease.

Renal Disease

Because there are so many facets to hypertension in renal disease, Chapter 9 covers that combination in depth.

Hypertension and Diabetes

The incidence of diabetes is rapidly rising in concert with obesity and physical inactivity (see Chapter 3). Most diabetics are hypertensive, and their hypertension

accelerates both cardiovascular and renal infirmities. Fortunately, control of hypertension can protect against both microvascular and macrovascular complications, perhaps even better than control of hyperglycemia (U.K. Prospective Diabetes Study, 1998a). As a consequence of both the added risk of even small rises in BP and the protection provided by reduction of elevated BP, antihypertensive treatment of diabetics with a BP higher than 130/85 mm Hg is now recommended (Guidelines Subcommittee, 1999; Joint National Committee, 1997). The goal of therapy is uncertain, particularly in view of data that the lower the BP, the greater the protection (Adler et al., 2000).

Therapy should include lifestyle modifications, in particular weight reduction by caloric restriction and exercise for the majority of diabetics whose disease is largely the consequence of obesity (Dengel et al., 1998). Even without weight loss, exercise improves insulin sensitivity (Wei et al., 1999). Tight control of hyperglycemia is essential (U.K. Prospective Diabetes Study, 1998a), and thiazolidinediones (glitazones) may provide additional antihypertensive efficacy by improving insulin sensitivity (Parulkar et al., 2001). Similarly, statins may also lower BP as they correct the dyslipidemia that commonly accompanies diabetes (Tonolo et al., 2000).

Choice of Antihypertensive Agents

Most authorities recommend starting with an ACEI, particularly if microalbuminuria is present (Bakris et al., 2000b), in view of the special benefits that this class of drug appears to provide for diabetic nephropathy (see Chapter 9). As good as they are, ACEIs may provoke three problems more frequently in diabetic than in nondiabetic hypertensives: (a) hypoglycemia (Morris et al., 1997); (b) hyperkalemia if hyporeninemic hypoaldosteronism is present (O'Keefe et al., 1999); and (c) renal failure if bilateral renal artery stenoses are not recognized (see Chapter 10).

Now that data from three RCTs (Brenner et al., 2001; Lewis et al., 2001; Parving et al., 2001) of the ARBs irbesartan and losartan in type 2 diabetics with nephropathy have been presented, an ARB can be used instead of an ACEI.

A diuretic is a logical second choice, avoiding the potential hazards of high doses noted in the past (Warram et al., 1991). Low-dose diuretic-based therapy provides equal protection for diabetics and nondiabetics alike (Lièvre et al., 2000).

A b-blocker (atenolol) was as effective as an ACEI (captopril) in the U.K. Prospective Diabetes Study (1998b), and certainly should be given to those with coronary disease, despite their propensity to worsen glycemia (Gress et al., 2000) and cause weight gain (Sharma et al., 2001). A CCB may be safely used (Tuomilehto et al., 1999), particularly to achieve the lower goal of therapy (<130/80 mm Hg) needed to protect these high-risk patients (Grossman et al., 2000).

For almost all diabetic hypertensives, two, three, or four antihypertensive drugs will be needed to achieve adequate BP control (Bakris et al., 2000b). Along with tight control of glycemia and lipids, these therapies will be difficult and expensive to provide, but their value is clear (Gæde et al., 1999) and cost effective (Elliott et al., 2000). When the data from all comparative trials of various drugs in almost 5,000 hypertensive diabetics are combined, the lowest mortality rate has been seen with CCB-based therapy (Kaplan, 2001b).

Insulin Sensitivity

The differences in insulin sensitivity noted by Lithell (1991) in nondiabetic hypertensives given various antihypertensives for 3 to 6 months (shown in Fig. 7-19) may or may not translate into significant differences in the long-term management of hypertensive diabetics. Significant improvements in insulin sensitivity and glucose tolerance have been observed to persist for 12 months after replacing b-blocker therapy with ACEI therapy (Berntorp et al., 1992). The improvement noted by Lithell with captopril has been observed with some other ACEIs (Feldman and Schmidt, 2001) but not all (Haenni et al., 1997).

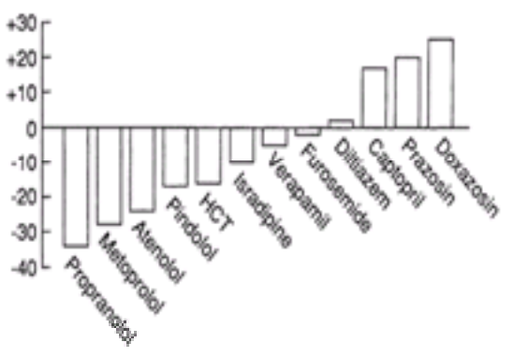


FIG. 7-19. The effects on insulin sensitivity index of 3 to 6 months of anti-hypertensive monotherapy given to groups of hypertensive patients. Data shown as percentage change. HCT, hydrochlorothiazide. (Modified from Lithell HO. Effect of antihypertensive drugs on insulin, glucose, and lipid metabolism. *Diabetes Care* 1991;14: 203–209.)

Hypertension and Obesity

Obesity is a major contributor to hypertension (see Chapter 3). The value of weight reduction was covered in Chapter 6. Obese hypertensives may be less responsive to various antihypertensive agents, and weight loss reduces the amount of medication needed to control hypertension (Jones et al., 1999). Weight loss may be more difficult to achieve when b-blockers are used (Sharma et al., 2001) but, if coronary disease is present, their use is clearly indicated.

Care should be taken with the use of appetite suppressants, particularly sympathomimetics (see Chapter 15). Hopefully, more therapies for obesity that do not adversely affect BP will become available.

Hypertension and Dyslipidemia

Three facts should be recognized in the relationship between hypertension and dyslipidemia. First, the two are more common together than is expected by chance (Goode et al., 1995), likely from the contributions of obesity, diabetes, and alcohol abuse. Dyslipidemia adds further to the endothelial dysfunction typical of hypertension (Maron et al., 2000).

Second, some drugs used to treat hypertension may have either beneficial or deleterious effects on serum lipids (Kasiske et al., 1995) (Table 7-21). Fortunately, these effects tend to be minimal and transient and, in appropriately low doses, tend not to interfere with the overall benefits of diuretic- or b-blocker–based therapies as regards cardiovascular morbidity and mortality (Brook, 2000). Nonetheless, the special ability of a-blockers to reduce lipids adds to their attractiveness (Papadakis et al., 1999).

Agent	Change in serum lipid (mmol per L)		
	Total cholesterol	HDL cholesterol	Triglycerides
Diuretic	0.13	No change	0.18
High-dose/beta	0.25/0.26	—	—
β-Blocker	No change	−0.10	0.35
α-Blocker	−0.20	0.02	−0.07
Central α-agonist	−0.21	−0.05	No change
Angiotensin-converting enzyme inhibitor	No change	No change	−0.07
Calcium channel blocker	No change	No change	No change
Vasodilator	−0.22	0.06	No change

HDL, high-density lipoprotein.
[a]Data from 474 clinical trials of 65 agents in >65,000 patients.
Reprinted from Kasiske BL, Ma JZ, Kalil RSN, Louis TA. Effects of antihypertensive therapy on serum lipids. Ann Intern Med 1995;122:133–141, with permission.

TABLE 7-21. *Effects of antihypertensive therapy on serum lipids*[a]

Third, treatment of dyslipidemia, in particular with statins, may have an independent effect of lowering BP (Borghi et al., 2001; Spósito et al., 1999). The current enthusiasm for the wider use of these drugs to treat dyslipidemia should only be heightened in patients with hypertension. Fortunately, no interferences with the actions of antihypertensive drugs or the effectiveness of the statins occur when they are used simultaneously (Chan et al., 1995). Therefore, the way is clear for a much wider attack on the combined threats of hypertension and dyslipidemia.

Sexual Dysfunction

Sexual dysfunction is common, even more in women than men (Laumann et al., 1999) and more in hypertensives than normotensives (Burchardt et al., 2000). The higher prevalence of sexual dysfunction in hypertensive men is likely related to lesser penile perfusion from atherosclerosis of penile arteries (Jensen et al., 1999), but psychological concerns (Araujo et al., 2000) and coexisting obstructive sleep apnea (Fanfulla et al., 2000) may contribute. The use of antihypertensive therapy may add to the problems in men (Grimm et al., 1997) but likely not in women (Duncan et al., 2000).

Effects of Antihypertensive Drugs

Antihypertensive drugs are considered to be among the most common causes of erectile dysfunction, but much of the effect may be a psychological reaction (Prisant et al., 1994). In addition, some drugs may cause retarded ejaculation (guanethidine), gynecomastia (spironolactone), and reduced desire for sex (spironolactone).

The best prospective data now available are from the 557 men and 345 women, aged 45 to 69, with a diastolic BP of 90 to 99 mm Hg, enrolled in TOMHS (Grimm et al., 1997). At baseline, 14.4% of men and 4.9% of women had sexual problems; 12.2% of the men had erectile dysfunction, whereas 2% of women had a problem having orgasm. On treatment—which included a reduction of weight, sodium, and alcohol along with more exercise for all—those men given the diuretic chlorthalidone, 15 mg per day, had double the incidence of erectile problems (17.1%) experienced by those on placebo (8.1%). Incidence was lowest (2.8%) with the a-blocker doxazosin and was similar to placebo with a b-blocker, ACEI, and CCB. Incidence of new sexual problems in women was low in all treatment groups.

If the problem develops or is made significantly worse after starting any antihypertensive drug, that drug should be stopped. If the patient's hypertension is fairly mild, therapy should be withheld until return of pretreatment sexual function. When it returns, a small dose of a drug from another class should be started in an attempt to lower the BP very slowly and gently. Some men will become impotent whenever the systemic BP is lowered very much; for them, medical or surgical management of erectile dysfunction may be required if the hypertension is to be controlled.

Treatment

The availability of sildenafil (Viagra) has had a major impact both on the willingness of male patients and physicians to discuss erectile dysfunction and on the ability to treat it (Chew et al., 2000).

Sildenafil often lowers systemic BP (Mahmud et al., 2001), but no increase in adverse effects was seen in a retrospective analysis of data from ten RCTs in which 1,218 men on various antihypertensive drugs were given the agent (Kloner et al., 2001). A case report has described an inhibition of sildenafil metabolism by the concomitant use of diltiazem, an inhibitor of the hepatic cytochrome P450 system, resulting in marked hypotension (Khoury and Kritharides, 2000).

Beyond common but relatively minor side effects (flushing, headache), the drug may potentiate the effect of nitrates used for treatment of coronary disease, inducing significant vasodilation and hypotension (Ishikura et al., 2000) and activating sympathetic nerves (Phillips et al., 2000).

For those who cannot tolerate sildenafil or who do not respond adequately to it, other options are available (Chew et al., 2000). One way or the other, erectile dysfunction can usually be overcome so that hypertensive men can do what is needed to control their hypertension while maintaining satisfactory sexual function.

Pilots Who Are Hypertensive

The U.S. Federal Aviation Administration has changed the regulations considerably as to the limits of BP and the types of antihypertensive medications that can be taken by people who wish to be certified as pilots. These regulations are given by the U.S. Department of Transportation (1999). The maximum permitted seated BP is 155/95 mm Hg. Most antihypertensive drugs can be used, with the exceptions of those that act centrally, including reserpine, guanethidine, guanadrel, methyldopa, and guanabenz.

Hypertension with Anesthesia and Surgery

Blood pressure should be well controlled before elective surgery. A preoperative history of hypertension increases the risk of perioperative mortality (Howell et al., 1996), and the prior administration of antihypertensive therapy reduces that risk (Bach, 1998). In a randomized trial, half of 112 high-risk patients undergoing vascular surgery were given the b-blocker bisoprolol, the other half-standard care (Poldermans et al., 1999). Bisoprolol provided a reduction in fatal and nonfatal cardiac events. Similar protection with atenolol had been seen in high-risk patients undergoing noncardiac surgery (Mangano et al., 1996). Those given 5 mg atenolol intravenously 30 minutes before surgery and every 12 hours thereafter or 50 to 100 mg atenolol by mouth for the next 7 days had a reduced mortality from cardiac causes and a higher 2-year event-free survival (83%) versus those given placebo (68%).

In commenting on that study, Eagle and Froehlich (1996) recommend that patients taking b-blockers preoperatively should continue to take them and, “if the preoperative evaluation shows clear or likely evidence of underlying CHD, and particularly if there is an additional reason to use a b-blocker such as concomitant hypertension, then it is probably appropriate to use b-blockers perioperatively.”

Whatever drugs hypertensive patients are taking before surgery should be continued until the time of surgery, using parenteral or transdermal forms if available (Bach, 1998). When any antihypertensive drug is stopped before surgery, severe hypertension may develop in the postoperative period, particularly with agents such as oral clonidine that have a propensity to rebound hypertension. The exception may be ARBs. In a small group of patients, hypotensive episodes occurred more frequently after anesthetic induction in those receiving an ARB than in those receiving b-blockers, CCBs, or ACEIs (Brabant et al., 1999). Subsequently, these same investigators reported a high incidence of severe hypotension in patients on an ARB undergoing general anesthesia and recommend that it be stopped the day before surgery (Bertrand et al., 2001). Those on a CCB may experience an increase in surgical bleeding (Zuccalá et al., 1997).

If hypertension needs to be treated during surgery, intravenous labetalol, nitroprusside, nicardipine, or esmolol can be used (Kross et al., 2000; Sugai et al., 1997).

For those in need of postoperative BP reduction, successful use of parenteral forms of various agents has been reported, including the short-acting b-blocker esmolol, labetalol, nicardipine (Halpern et al., 1992), or enalaprilat (Boldt et al., 1995). Sublingual nifedipine is inappropriate, because it does not allow for the control provided by parenteral agents.

Postoperatively, significant lowering of BP may occur as a nonspecific response to surgery and may persist for months (Volini and Flaxman, 1939). Do not be deceived by what appears to be an improvement in the patient's hypertension: Anticipate a gradual return to preoperative levels.

Special problems in postoperative patients after coronary bypass surgery, trauma, and burns are covered in Chapter 15. Anesthetic considerations in patients with pheochromocytoma are covered in Chapter 12.

Paroxysmal Hypertension and Hypovolemia

Cohn (1966) reported on a group of patients who were severely hypertensive and rapidly went into peripheral vascular collapse when treated with antihypertensive agents. These patients were hypovolemic, and their initial hypertension was at least partly a reflection of compensatory sympathetic nervous system overactivity and an activated renin-angiotensin system. When their compensatory support was removed by treatment, profound hypotension quickly followed. Similar patients have been observed to have a fall in BP as their shrunken fluid volume is replaced, quieting their activated sympathetic nervous and renin-angiotensin systems (Bissler et al., 1991).

CONCLUSION

The large numbers of drugs now available can be used to treat virtually every hypertensive patient successfully under most any circumstance. Even those at highest risk—the few who develop a hypertensive emergency—can be effectively treated, as is shown in the next chapter.

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8
Hypertensive Crises

Although only a small spot in the large panorama of hypertension, hypertensive crises represent, on one hand, the most immediate danger to those afflicted and, on the other, the most dramatic proof of the life-saving potential of antihypertensive therapy. Such crises are less likely now to be the end result of chronic hypertension but may be seen at any age, representing the manifestations of suddenly developing hypertension from such diverse causes as substance abuse, immunosuppressive drugs, and human immunodeficiency virus infection (Vaughn and Delanty, 2000). Not surprisingly, those that reflect inadequate management of long-standing primary hypertension are seen primarily among the uninsured who receive inadequate health care (Kadiri et al., 2000).

DEFINITIONS

A *hypertensive emergency* is a situation that requires immediate reduction in blood pressure (BP) with parenteral agents because of acute or progressing target organ damage (Table 8-1).

Accelerated-malignant hypertension with papilledema
Cerebrovascular conditions
Hypertensive encephalopathy
Atherothrombotic brain infarction with severe hypertension
Intracerebral hemorrhage
Subarachnoid hemorrhage
Head trauma
Cardiac conditions
Acute aortic dissection
Acute left ventricular failure
Acute or impending myocardial infarction
After coronary bypass surgery
Renal conditions
Acute glomerulonephritis
Renovascular hypertension
Renal crisis from collagen-vascular disease
Severe hypertension after kidney transplantation
Excess circulating catecholamines
Pheochromocytoma crisis
Food or drug interactions with monoamine oxidase inhibitors
Sympathomimetic drug use (cocaine)
Rebound hypertension after sudden cessation of antihypertensive drugs
Autonomic hyperreflexia after spinal cord injury
Eclampsia
Surgical conditions
Severe hypertension in patients requiring immediate surgery
Postoperative hypertension
Postoperative bleeding from vascular suture lines
Severe body burns
Severe epistaxis
Thrombotic thrombocytopenic purpura

TABLE 8-1. *Hypertensive emergencies*

A *hypertensive urgency* is a situation with markedly elevated BP but without severe symptoms or progressive target organ damage, wherein the BP should be reduced within hours, often with oral agents. Some of the circumstances listed in Table 8-1 may be urgencies rather than emergencies if of lesser severity. These include some patients with accelerated-malignant hypertension, perioperative or rebound hypertension, less severe body burn, or epistaxis. The distinction between an emergency and an urgency is often ambiguous. Perhaps the wiser distinction is to consider all patients in need of immediate institution of antihypertensive treatment as emergencies, leaving the type and route of therapy to clinical judgment and local resources.

On the other hand, the presence of markedly elevated BP in the absence of symptoms or target organ damage should not be considered an emergency but rather as an indication for relief of precipitating causes (e.g., anxiety, hypoxia, pain) and, if still needed, the use of oral drug therapy to bring the BP down to a safer level.

Accelerated-malignant hypertension represents markedly elevated BP with papilledema (grade 4 Keith-Wagener retinopathy) and/or hemorrhages and exudates (grade 3 Keith-Wagener retinopathy). The funduscopic differences do not connote different clinical features or prognosis (Ahmed et al., 1986).

Hypertensive encephalopathy is a sudden, marked elevation of BP with severe headache and altered mental status, reversible by reduction of BP. Encephalopathy is more common in previously normotensive individuals whose pressures rise suddenly, such as during pregnancy with eclampsia; the accelerated-malignant course often appears without encephalopathy in individuals with more chronic hypertension whose pressures progressively rise.

ACCELERATED-MALIGNANT HYPERTENSION

Mechanisms

The cascade from critical levels of hypertension to vascular damage and tissue ischemia is depicted in Figure 8-1. When BP reaches some critical level—in experimental animals at a mean arterial pressure of 150 mm Hg—lesions appear in arterial walls, and the syndrome of accelerated-malignant hypertension begins (Fig. 8-1). This may be provoked by one or more vasoactive factors, but the accelerated-malignant phase is likely to be a nonspecific consequence of very high BP (Beilin and Goldby, 1977). Any form of hypertension may progress to the accelerated-malignant phase, some without activation of the reninangiotensin system or other humoral mechanisms (Gavras et al., 1975a).

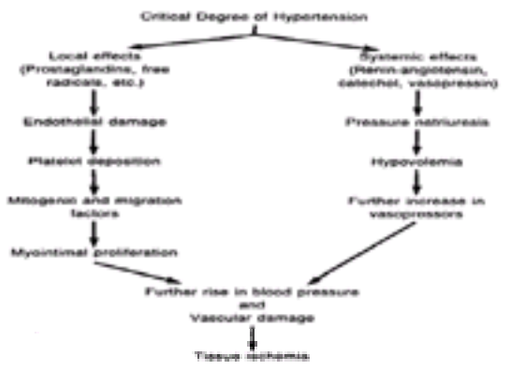

FIG. 8-1. Scheme for initiation and progression of accelerated-malignant hypertension.

Structural Changes

In animal models, the level of the arterial pressure correlates closely with the development of fibrinoid necrosis, the experimental hallmark of accelerated-malignant hypertension (Byrom,1974). In humans, fibrinoid necrosis is rare, perhaps because those who die from an acute attack have not had time to develop the lesion and those who live with therapy are able to repair it. The typical lesions, best seen in the kidney, are hyper-plastic arteriosclerosis and accelerated glomerular obsolescence (Kitiyakara and Guzman, 1998). In blacks, myointimal hyperplasia appears to be the typical renal lesion (Pitcock et al., 1976).

Humoral Factors

There is support, however, for the involvement of factors besides the level of the BP in setting off the accelerated-malignant phase, particularly as the range of pressures in patients with severe “benign” hypertension and accelerated-malignant hypertension may overlap (Kincaid-Smith, 1991). As shown on the right side of Figure 8-1, in both rats (Gross et al., 1975) and dogs (Dzau et al., 1981) with unilateral renal artery stenosis, the accelerated-malignant phase was preceded by natriuresis that markedly activated the reninangiotensin system. The progression was delayed by giving saline loads after the natriuresis.

Whether these animal models involving a major insult to renal blood flow are applicable to most human accelerated-malignant hypertension is uncertain; however, renal artery stenosis is a common cause of accelerated-malignant hypertension in humans, found in 20% to 35% of patients with this form of hypertension (Davis et al., 1979; Webster et al., 1993).

Evidence for the pathway shown on the left side of Figure 8-1 comes from studies on cats made acutely and severely hypertensive (Kontos, 1985). Other pressor mechanisms, including endothelin-1 (Yoshida et al., 1994), may be involved as well as the suppression of vasodepressors, as reflected in decreased urinary kallikrein excretion (Hilme et al., 1993).

Functional autoantibodies against a $_1$-adrenergic receptors (Fu et al., 1994) and angiotensin II receptors (Fu et al., 2000) have been found in some patients; whether they reflect a primary autoimmune mechanism or secondary vascular damage is uncertain. Plasma markers of endothelial dysfunction (von Willebrand factor), platelet activation (soluble P-selectin) and coagulopathy (fibrinogen) are often present (Edmunds et al., 2000).

The development of accelerated-malignant hypertension has been observed to be more common in cigarette smokers (Isles et al., 1979). Moreover, an exaggerated pressor response to smoking and drinking coffee has been noted in such patients (Freestone et al., 1995).

Clinical Features

Accelerated-malignant hypertension may be accompanied by various symptoms and signs (Table 8-2). However, it is not uncommon to see patients, particularly young black men, who deny any prior symptoms when seen in the end stages of the hypertensive process, with their kidneys destroyed, heart failing, and brain function markedly impaired. Even in the elderly, hypertension may initially present in the accelerated-malignant phase (Lip et al., 2000).

Blood pressure: usually >140 mm Hg diastolic
Funduscopic findings: hemorrhages, exudates, papilledema
Neurologic status: headache, confusion, somnolence, stupor, vision loss, focal deficits, seizures, coma
Renal status: oliguria, azotemia
Gastrointestinal status: nausea, vomiting

TABLE 8-2. *Clinical characteristics of accelerated-malignant hypertension*

Less common clinical presentations include:

- Fibrinoid necrosis within abdominal arteries producing major gastrointestinal tract infarction with an acute abdomen (Padfield, 1975).
- Acute pancreatitis (Mathur and Warren, 1989).
- Rapidly progressive necrotizing vasculitis (Mitchell, 1994).

Funduscopic Findings

The effects of the markedly elevated BP are displayed in the optic fundi (Fig. 8-2). Beyond the chronic arteriolar sclerosis and hypertrophy, acute changes may include arteriolar spasm, either segmental or diffuse; retinal edema, with a sheen or ripples; retinal hemorrhages, either superficial and flame-shaped or deep and dot-shaped; retinal exudates, either hard and waxy from resorption of edema or with a raw cotton appearance from ischemia; and papilledema and engorged retinal veins.

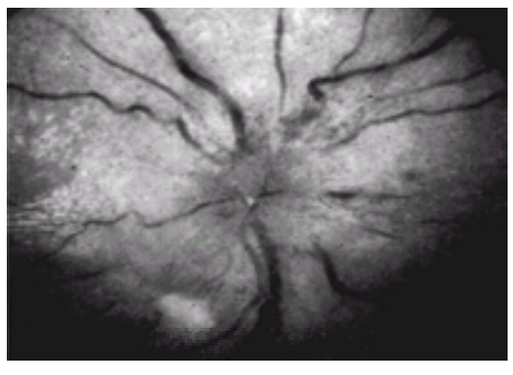

FIG. 8-2. Funduscopic photography showing typical features of accelerated-malignant hypertension.

Similar retinopathy with hemorrhages and even papilledema rarely occurs in severe anemia, collagen diseases, and subacute bacterial endocarditis. Some patients have pseudopapilledema associated with congenital anomalies, hyaline bodies (drusen) in the disc, or severe farsightedness. Fluorescein fundus photography will distinguish between the true and the pseudo states. In addition, benign intracranial hypertension may produce real papilledema but is usually a minimally symptomatic and self-limited process (Jain and Rosner, 1992).

Evaluation

In addition to an adequate history and physical examination, a few laboratory tests should be done immediately to assess the patient's status (Table 8-3).

History
Prior diagnosis and treatment of hypertension
Intake of pressor agents: street drugs, sympathomimetics
Symptoms of cerebral, cardiac, and visual dysfunction
Physical examination
Blood pressure
Funduscopy
Neurologic status
Cardiopulmonary status
Body fluid volume assessment
Peripheral pulses
Laboratory evaluation
Hematocrit and blood smear
Urine analysis
Automated chemistry: creatinine, glucose, electrolytes
Electrocardiogram
Plasma renin activity and aldosterone (if primary aldosteronism is suspected)
Plasma renin activity before and 1 h after 25 mg captopril (if renovascular hypertension is suspected)
Spot urine or plasma for metanephrine (if pheochromocytoma is suspected)
Chest radiograph (if heart failure or aortic dissection is suspected)

TABLE 8-3. *Initial evaluation of patients with a hypertensive emergency*

Laboratory Findings

Hematology and Urine Analysis

Microangiopathic hemolytic anemia with red cell fragmentation and intravascular coagulation may occur in accelerated-malignant hypertension, possibly originating from the fibrinoid necrotic arterial lesions (Gavras et al., 1975b).

The urine contains protein and red cells. In a few patients, acute oliguric renal failure may be the presenting manifestation (Lip et al., 1997).

Blood Chemistry

Various features of renal insufficiency may be present. Approximately half of patients have hypokalemia, reflecting secondary aldosteronism from increased renin secretion induced by intrarenal ischemia (Kawazoe et al., 1987). Hyponatremia is usual, in contrast to the hypernatremia found in primary aldosteronism.

Cardiography

The electrocardiogram usually displays evidence of left ventricular hypertrophy, strain, and lateral ischemia. Echocardiography may show incoordinate contractions with impaired diastolic function and delayed mitral valve opening (Shapiro and Beevers, 1983).

Evaluation for Identifiable Causes

Once causes for the presenting picture other than severe hypertension are excluded and necessary immediate therapy is provided, an appropriate evaluation for identifiable causes of the hypertension should be performed as quickly as possible. It is preferable to obtain necessary blood and urine samples for required laboratory studies before institution of therapies that may markedly complicate subsequent evaluation. None of these procedures should delay effective therapy.

Renovascular Hypertension

Renovascular hypertension is by far the most likely secondary cause and, unfortunately, the one that may be least obvious by history, physical examination, and routine laboratory tests. It should be particularly looked for in older patients with extensive atherosclerosis (see Chapter 10).

As described in Chapter 10, a single-dose captopril challenge test, measuring plasma renin activity before and 1 hour after administration of 25 mg captopril, can be performed when the patient presents, because the captopril will almost certainly lower the BP during the subsequent hour, protecting the patient while helping to rule out—or in—renovascular hypertension.

Pheochromocytoma

If there are suggestive symptoms, a plasma or spot urine sample should be collected for metanephrine assay, because most catechol measurements may be invalidated by labetalol and other antihypertensive drugs.

Primary Aldosteronism

If significant hypokalemia is noted on the initial blood test, a plasma renin and aldosterone level should be obtained.

Prognosis

If untreated, most patients with accelerated-malignant hypertension will die within 6 months. The 1-year survival rate was only 10% to 20% without therapy (Dustan et al., 1958). With current therapy, 5-year survival rates of greater than 70% are usual (Lip et al., 2000; Sugiyama and Sesoko, 1992; Webster et al., 1993), clearly

showing the major protection provided by antihypertensive therapy.

Renal Function and Prognosis

Many patients when first seen with accelerated-malignant hypertension have significant renal damage, which markedly worsens their prognosis (Lip et al., 1997). In one series of 100 consecutive patients with malignant hypertension (Bing et al., 1986), the 5-year survival rate of those without renal impairment (serum creatinine <1.5 mg per dL) was 96%, no different from that of the general population. However, among those with renal impairment, 5-year survival fell to 65%. When vigorous antihypertensive therapy is begun, renal function often worsens transiently, but in nearly half of those with initial renal insufficiency, function remains invariant or improves (Lip et al., 1997). Of 54 patients with malignant hypertension requiring dialysis, 12 recovered sufficient renal function to allow withdrawal of dialysis (James et al., 1995).

Causes of Death

Therapy used over the last 50 years has dramatically reduced immediate deaths from acute renal failure, hemorrhagic strokes, and congestive heart failure. With longer survival, death from an acute myocardial infarction is more likely (Webster et al., 1993), but death from renal failure is still common in those who present with an elevated serum creatinine (Lip et al., 2000).

HYPERTENSIVE ENCEPHALOPATHY

With or without the structural defects of accelerated-malignant hypertension, progressively higher BP can lead to hypertensive encephalopathy.

Pathophysiology

Breakthrough Vasodilation

With changes in BP, cerebral vessels dilate or constrict to maintain a relatively constant level of cerebral blood flow (CBF), the process of autoregulation that is regulated by sympathetic nervous activity (Tuor, 1992). Figure 8-3 shows direct measurements taken in cats, with progressive vasodilation as pressures are lowered and progressive vasoconstriction as pressures rise (MacKenzie et al., 1976). Note, however, that when mean arterial pressures reach a critical level, approximately 180 mm Hg, the previously constricted vessels, unable to withstand such high pressures, are stretched and dilated—first in areas with less muscular tone, producing irregular sausage-string patterns, and later diffusely, producing generalized vasodilation. This vasodilation allows a breakthrough of CBF, which hyperperfuses the brain under high pressure, with leakage of fluid into the perivascular tissue, leading to cerebral edema and the clinical syndrome of hypertensive encephalopathy (Strandgaard and Paulson, 1989).

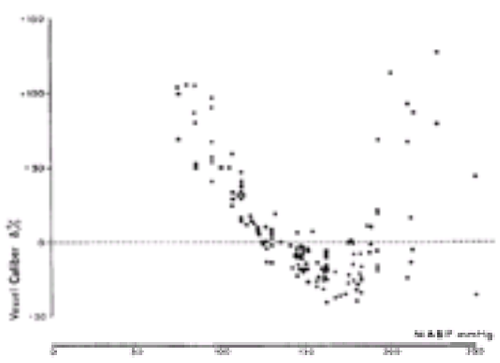

FIG. 8-3. Observed change in the caliber of pial arterioles with a caliber of less than 50 mm in eight cats, calculated as a percentage of change from the caliber at a mean arterial blood pressure (MABP) of 135 mm Hg. The blood pressure was raised by intravenous infusion of angiotensin II. (Reprinted from MacKenzie ET, Strandgaard S, Graham DI, et al. Effects of acutely induced hypertension in cats on pial arteriolar caliber, local cerebral blood flow, and the blood-brain barrier. Circ Res 1976;39:33, with permission.)

Breakthrough vasodilation has also been demonstrated in humans (Strandgaard et al., 1973). Figure 8-4 shows curves of autoregulation constructed by measuring CBF repetitively while arterial BP was lowered by vasodilators or raised by vasoconstrictors. CBF is constant between mean arterial pressures of 60 and 120 mm Hg in normotensive subjects. However, when pressure was raised beyond the limit of autoregulation, breakthrough hyperperfusion occurred.

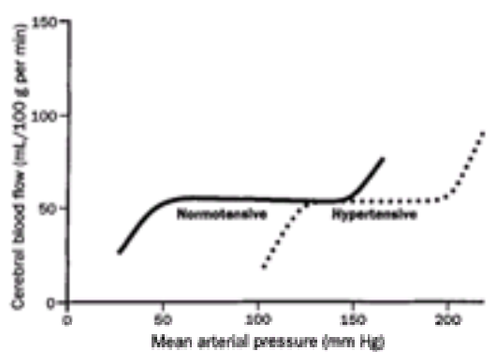

FIG. 8-4. Idealized curves of cerebral blood flow at varying levels of systemic blood pressure in normotensive and hypertensive subjects. Right-ward shift in autoregulation is shown with chronic hypertension. (Adapted from Strandgaard S, Olesen J, Skinhøj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. BMJ 1973;1:507–510 .)

Pressures such as these are handled without obvious trouble in chronic hypertensives, whose blood vessels adapt to the chronically elevated BP with structural thickening, presumably mediated by sympathetic nerves (Tuor, 1992). Thereby the entire curve of autoregulation is shifted to the right (Fig. 8-4). Even with this shift, breakthrough will occur if mean arterial pressures are markedly raised to levels beyond 180 mm Hg.

These findings explain a number of clinical observations. Previously normotensive people who suddenly become hypertensive may develop encephalopathy at relatively low levels of hypertension, which are nonetheless beyond their upper limit of autoregulation. These include children with acute glomerulonephritis and young women with eclampsia. On the other hand, chronically hypertensive patients less commonly develop encephalopathy and only at much higher pressures.

In regard to the lower portion of the curve, when the BP is lowered by antihypertensive drugs too quickly, chronic hypertensives often are unable to tolerate the reduction without experiencing cerebral hypoperfusion, manifested by weakness and dizziness. These symptoms may appear at levels of BP that are still well within the normal range of autoregulation and well tolerated by normotensives. The reason is that the entire curve of autoregulation shifts, so that the lower end also is moved, with a fall-off of CBF at levels of 100 to 120 mm Hg mean arterial pressure (Fig. 8-4). Moreover, chronic hypertensives may lose their ability to autoregulate, increasing their risk of cerebral ischemia when BP is lowered acutely (Jansen et al., 1987).

As detailed in Chapter 7, if the BP is lowered gradually, the curve can shift back toward normal so that greater reductions in pressure can eventually be tolerated. However, maneuvers that increase CBF further and thereby increase intracranial pressure, such as CO_2 inhalation or cerebral vasodilators (e.g., hydralazine and nitroprusside), may be harmful in patients with encephalopathy.

Central Nervous System Changes

Encephalopathic patients have many of the same laboratory findings seen in patients with malignant hypertension, but they have more central nervous system manifestations. The cerebrospinal fluid rarely shows pleocytosis (McDonald et al., 1993) but is usually under increased pressure. Electroencephalography may show varied, transient, focal, or bilateral disturbances (Torocsik et al., 1999). Computed tomography or magnetic resonance imaging shows a characteristic posterior leukoencephalopathy predominantly affecting the parietooccipital white matter, often the cerebellum and brainstem, and occasionally other areas as well (Schwartz et al., 1998; Vaughan and Delanty, 2000).

Differential Diagnosis

There are clinical situations in which the BP is elevated and the patient has findings that suggest hypertension-induced target organ damage wherein the findings are unrelated to the elevated BP. Table 8-4 lists conditions that may mimic a hypertensive emergency. A less aggressive approach to lowering of the BP is indicated in such patients. Particular caution is warranted after a stroke, when a rapid decrease in BP may shunt blood away from the ischemic area and extend the lesion (Brott and Bogousslavsky, 2000). The fact that stroke usually presents abruptly, whereas hypertensive encephalopathy usually develops more gradually, may aid in the differentiation.

Acute left ventricular failure
Uremia, particularly with volume overload
Cerebrovascular accident
Subarachnoid hemorrhage
Brain tumor
Head injury
Epilepsy (postictal)
Collagen diseases, particularly systemic lupus, with cerebral vasculitis
Encephalitis
Drug ingestion: sympathomimetics (e.g., cocaine)
Acute intermittent porphyria
Hypercalcemia
Acute anxiety with hyperventilation syndrome or panic attack

TABLE 8-4. *Conditions that may mimic a hypertensive emergency*

In addition to the two specific presentations of accelerated-malignant hypertension and hypertensive encephalopathy, hypertension may be life threatening when it accompanies cerebral, cardiac, and other acute conditions wherein a markedly elevated BP contributes to the ongoing tissue damage (Table 8-1). The role of hypertension in most of these conditions is covered in Chapter 4, and some of the other specific circumstances (e.g., pheochromocytoma crises and eclampsia) are covered in their respective chapters. Therapy for some of these specific conditions is covered later in this chapter.

THERAPY FOR HYPERTENSIVE EMERGENCIES

The majority of patients with the conditions shown in Table 8-1 require immediate reduction in BP. Some patients, such as those with hypertensive encephalopathy, must be treated quickly. If the pressure is not reduced, cerebral edema will worsen, and the lack of autoregulation in ischemic brain tissue may result in further increases in the volume of the ischemic tissue, which may cause either acute herniation or more gradual compression of normal brain. Moreover, with increased intracranial pressure, the Cushing reflex, which causes the systemic pressure to rise further in an attempt to maintain CBF, may be activated (Jones, 1989).

On the other hand, the shift to the right of the curve of cerebral autoregulation in most patients who develop encephalopathy exposes them to the hazards of a fall in CBF when systemic pressure is lowered abruptly by more than approximately 25%, even though these levels are not truly hypotensive (Strandgaard and Paulson, 1996) (Fig. 8-4). Symptoms of cerebral ischemia may not develop, however, because the brain can extract additional oxygen when perfusion is reduced. Moreover, the lower limit of autoregulation may be shifted back to the left by the action of agents such as angiotensin-converting enzyme inhibitors and a-blockers, which dilate large cerebral arteries and increase downstream pressure, causing smaller resistance vessels to constrict (Barry, 1989).

Initiating Therapy

With encephalopathy or evidence of progressive myocardial ischemia, no more than a very few minutes should be taken to admit a patient to an intensive care unit, set up intravenous access, and begin frequent monitoring of the BP, usually with an intraarterial line. The initial blood and urine samples should be obtained, and antihypertensive therapy should begin immediately thereafter.

Monitoring Therapy

Abrupt falls in pressure should be avoided, and the goal of immediate therapy should be to lower the diastolic pressure only to approximately 110 mm Hg. The reductions may need to be even less if signs of tissue ischemia develop as the pressure is lowered. Most of the catastrophes seen with treatment of hypertensive emergencies were related to overly aggressive reduction of the BP (Jansen et al., 1987).

Particular care should be taken in elderly patients and in patients with known cerebrovascular disease, who are even more vulnerable to sudden falls in systemic BP (Fischberg et al., 2000). As described in Chapter 7, patients with acute stroke should have their BP brought down only if it is extremely high and contributing to the neurologic damage, as in the presence of encephalopathy, or before the use of thrombolytic therapy (Brott and Bogousslavsky, 2000).

If the neurologic status worsens as treatment proceeds, intracranial pressure may be markedly elevated, most likely from the cerebral edema associated with the hypertensive emergency but also, possibly, by the further increase in CBF invoked by antihypertensive drugs such as hydralazine (Schroeder and Sillesen, 1987) or nitroprusside (Cottrell et al., 1978), which dilate cerebral vessels. In this situation, urgent computed tomography of the brain should be obtained and, if potentially life-threatening cerebral edema is identified, osmotic diuresis with mannitol, often plus intravenous furosemide, can be effective (Brott and Bogousslavsky, 2000).

Parenteral Drugs

Table 8-5 lists the choices of parenteral therapy now available. It includes some that may be used for most conditions and others that should be reserved for specific indications. All are capable of inducing hypotension, a risk that mandates careful monitoring of BP. They are covered in the order shown in Table 8-5.

Drug[a]	Dose	Onset of action	Duration of action	Adverse effects[b]	Special indications
Diuretics					
Furosemide	20–40 mg i.v. 1–2 min, repeated and higher doses with renal insufficiency	5–15 min	2–3 h	Volume depletion, hypokalemia	Usually needed to maintain efficacy of other drugs
Vasodilators					
Nitroprusside (Nipride, Nitropress)	0.25–10.00 μg/kg/min as i.v. infusion	Immediate	1–2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or azotemia
Nitroglycerin (Nitro-Bid IV)	5–100 μg/min as i.v. infusion	2–5 min	5–10 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Fenoldopam (Corlopam)	0.1–0.8 μg/kg/min as i.v. infusion	4–5 min	10–15 min	Reflex tachycardia, increased intraocular pressure, headache	Renal insufficiency, after surgery
Nicardipine[c] (Cardene IV)	5–15 mg/h i.v.	5–10 min	1–4 h	Headache, nausea, flushing, tachycardia, focal phlebitis	Most hypertensive emergencies; caution with acute heart failure
Hydralazine (Apresoline)	10–20 mg i.v. 10–20 mg IM	10–20 min 20–30 min	3–8 h	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia; caution with high intracranial pressure
Enalaprilat (Vasotec IV)	1.25–5.00 mg every 6 h	15 min	6 h	Precipitous fall in pressure in high-renin states, response variable	Acute left ventricular failure
Adrenergic inhibitors					
Phentolamine	5–15 mg i.v.	1–2 min	3–10 min	Tachycardia, flushing, headache	Catecholamine excess
Carvedilol (Coreg)	200–500 μg/kg/min for 1 min, then 50–300 μg/kg/min i.v.	1–2 min	10–20 min	Hypotension, nausea	Aortic dissection, after operation
Labetalol (Normodyne, Trandate)	20–80 mg i.v. bolus every 10 min 2 mg/min i.v. infusion	5–10 min	3–6 h	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure

[a] In order of rapidity of action.
[b] Hypotension may occur with any.
[c] Intravenous formulations of other calcium channel blockers are also available.

TABLE 8-5. *Parenteral drugs for treatment of hypertensive emergency*

Diuretics

A potent diuretic, usually furosemide, is often initially given intravenously. In one controlled trial involving 64 patients with hypertensive encephalopathy and diastolic pressure above 135 mm Hg, 40 mg intravenous furosemide alone brought the pressure down from an average of 225/144 to 166/102 mm Hg over 5 hours in 12 patients (McNair et al., 1986). The remaining 52 patients still had a diastolic pressure higher than 125 mm Hg 1 hour after the furosemide; they were given additional therapy.

Even if not given initially, a diuretic will likely be needed after other antihypertensives are used, because reactive renal sodium retention usually accompanies a fall in pressure and may blunt the efficacy of nondiuretic agents.

On the other hand, if the patient is volume-depleted from pressure-induced natriuresis and prior nausea and vomiting, additional diuresis could be dangerous. In a few documented instances, volume expansion with intravenous saline has been shown to lower the BP (Baer et al., 1977; Kincaid-Smith, 1973). Most of the patients whose BP improved with salt repletion have had chronic renal disease; it is likely that they had prior salt-wasting interstitial nephritis, as seen with analgesic nephropathy.

Nitroprusside

Clinical Use

The BP always falls when nitroprusside is given, although it occasionally takes much more than the usual starting dose of 0.25 μg per kg per minute for a response. The antihypertensive effect disappears within minutes after the drug is stopped. Obviously, the drug should be used only with constant monitoring of the BP. A computer-controlled regulator of the rate of infusion has been described (Martin et al., 1992), and a commercially available unit—Titrator Model 10K (IVAC Corp., San Diego, CA)—has been found to improve the management of postoperative hypertension markedly in a controlled trial (Chitwood et al., 1992). Nitroprusside has been delivered intrathecally for relief of delayed cerebral vasoconstriction after subarachnoid hemorrhage (Thomas et al., 1999).

Mechanism of Action

This exogenous nitrate apparently acts in the same manner as the endogenous endotheliumderived relaxing factor, nitric oxide. The drug is a direct arteriolar and venous dilator and has no effect on the autonomic or central nervous system (Shepherd and Irvine, 1986). The venous dilation reduces blood return to the heart, causing a fall in cardiac output and stroke volume despite an increase in heart rate, while the arteriolar dilation prevents any rise in peripheral resistance, as would be expected when cardiac output falls (Brush et al., 1989). Nitroprusside may cause redistribution of blood flow away from ischemic areas and could increase the extent of myocardial damage in patients with coronary disease (Mann et al., 1978).

By dilating large cerebral arteries, nitroprusside may increase CBF and thereby increase intracranial pressure (Cottrell et al., 1978). However, the fall in systemic pressure moderates the rise in CBF, and most patients with encephalopathy respond well.

Metabolism and Toxicity

Nitroprusside is metabolized to cyanide by sulfhydryl groups in red cells, and the cyanide is rapidly metabolized to thiocyanate in the liver (Schulz, 1984). If high levels of thiocyanate (>10 mg per dL) remain for days, toxicity may be manifested as fatigue, nausea, disorientation, and psychosis. If cyanide toxicity is suspected because of metabolic acidosis and venous hyperoxemia, nitroprusside should be discontinued, and 4 to 6 mg of 3% sodium nitrite should be given intravenously over 2 to 4 minutes, followed by an infusion of 50 mL of 25% sodium thiosulfate (Gifford, 1991). Cyanide toxicity has been prevented by concomitant administration of hydroxocobalamin (Zerbe and Wagner, 1993).

Nitroglycerin

Intravenous nitroglycerin is being used increasingly for coronary vasodilation in patients with myocardial ischemia with or without severe hypertension. It reduces cardiac output (Lambert et al., 1993) and, like nitroprusside, it causes cerebral vasodilation and can increase intracranial pressure (Dahl et al., 1989). Methemoglobin is formed during the administration of all organic nitrates, but its mean concentration in patients receiving nitroglycerin for 48 hours or longer averaged only 1.5%, with no clinical symptoms (Kaplan et al., 1985).

Fenoldopam

Fenoldopam, a peripheral dopamine-I agonist, unlike other parenteral antihypertensive agents, maintains or increases renal perfusion while it lowers BP (Tumlin et al., 2000). It has been found to maintain most of its efficacy for 48 hours of constant rate infusion without rebound hypertension when discontinued (Taylor et al., 1999).

Fenoldopam may be safely used in all hypertensive emergencies and likely will be especially beneficial in patients with renal insufficiency. After a starting dose of 0.1 μg per kg per minute, the dose is titrated, depending on the BP response, at 15-minute intervals.

Nicardipine and Other Calcium Channel Blockers

When given by continuous infusion, the intravenous formulations of various dihydropyridine calcium channel blockers (CCBs) produce a steady, progressive fall in BP with little change in heart rate and a small increase in cardiac output (Risler et al., 1998). Nicardipine has been found to provide responses virtually equal to those seen with nitroprusside, with few side effects (Neutel et al., 1994). Other intravenous CCBs also are effective, including verapamil (Brush et al., 1989). Nimodipine, with an apparently greater selectivity for cerebral vessels, has been approved for use in relieving the vasospasm that accompanies subarachnoid hemorrhage (Wong and Haley, 1990).

Hydralazine

The direct vasodilator hydralazine can be given by repeated intramuscular injections as well as intravenously with a fairly slow onset and prolonged duration of action, allowing for less intensive monitoring. Significant compensatory increases in cardiac output preclude its use as a sole agent except in young patients, as with preeclampsia, who can handle the increased cardiac work without the likelihood that coronary ischemia will be induced. Hydralazine's primary use is for severe

hypertension during pregnancy.

Enalaprilat

Enalaprilat, the intravenous preparation of the active, free form of the prodrug enalapril, may be used for treatment of hypertensive emergencies wherein angiotensin-converting enzyme (ACE) inhibition is thought to offer special advantages, such as in severe congestive heart failure (Varriale et al., 1993). An initial dose of 0.625 mg is as effective as larger doses and may be less likely to induce severe hypotension in those with high renin-angiotensin levels (Hirschl et al., 1997). Apparently unique effects of ACE inhibitors (ACEIs) on cerebral autoregulation, resetting the autoregulatory curve to a lower pressure level, could protect against cerebral ischemia if pressure is lowered abruptly and markedly (Barry, 1989).

Phentolamine

The a-blocker phentolamine is specifically indicated for pheochromocytoma or tyramineinduced catecholamine crisis.

Esmolol

Esmolol, a relatively cardioselective b-blocker, is rapidly metabolized by blood esterases and has a short (approximately 9-minute) half-life and total duration of action (approximately 30 minutes). Its effects begin almost immediately, and it has found particular use during anesthesia to prevent postintubation hemodynamic perturbations (Oxorn et al., 1990).

Labetalol

The combined a- and b-blocker labetalol has been found to be both safe and effective when given intravenously either by repeated bolus (Huey et al., 1988) or by continuous infusion (Leslie et al., 1987) and is considered by Strandgaard and Paulson (1996) to be the drug of choice for immediate reduction of BP, because it will not raise intracranial pressure, as may direct vasodilators. It starts acting within 5 minutes, and its effects last for 3 to 6 hours. Labetalol can likely be used in almost any situation requiring parenteral antihypertensive therapy, except when left ventricular dysfunction could be worsened by the predominant b-blockade. On the other hand, carvedilol, another a- and b-blocker with different properties, has been found to be beneficial in congestive heart failure (Australia/New Zealand Heart Failure Research Collaborative Group, 1997). Caution is needed to avoid postural hypotension if patients are allowed out of bed. Nausea, itching, tingling of the skin, and b-blocker side effects may be noted.

Other Drugs

Urapidil, an a-blocker with additional central actions, has been found to be effective (Hirschl et al., 1996), but it is not available in the United States. Diazoxide, trimethaphan, intramuscular reserpine, and intravenous methyldopa are now obsolete.

Oral and Sublingual Agents

The same agents described in the section Therapy for Hypertensive Urgencies (later in this chapter), for oral or sublingual use have also been recommended for treatment of hypertensive emergencies. As Murphy (1995) notes, the rationale for the use of oral drugs is that they are easier to administer and equally as effective as parenteral agents. Both of these reasons are wrong. As Murphy (1995) states, “In the context of hypertensive emergencies, regardless of the agent chosen, equally close scrutiny is mandatory to detect early symptoms or signs” of target organ damage. Oral agents are both less effective and more likely to cause precipitous falls in BP, as the medications cannot be titrated. Therefore, if a hypertensive emergency exists, it should be treated with a parenteral agent unless circumstances preclude such therapy.

Criteria for Drug Selection

Because no clinical comparisons are available of the eventual outcome after the use of various agents, the choice of therapy is based on rapidity of action, ease of administration, and propensity for side effects. Although nitroprusside has been most widely used and continues to be preferred for most hypertensive emergencies by most authors, its propensity to increase intracranial pressure and the need for constant monitoring support the wider use of other effective parenteral agents such as labetalol, nicardipine, and fenoldopam.

Therapy for Specific Hypertensive Emergencies

Although specific drugs have been recommended for various types of hypertensive emergencies, there are really only a few situations in which one or another has been shown to be more or less useful.

Cerebrovascular Accidents

Caution is advised in lowering even markedly elevated BP in patients in the immediate post-stroke period (Gubitz and Sandercock, 2000). In the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study, the use of antihypertensive therapy in those who were hypertensive before thrombolysis was associated with less favorable outcomes (Brott et al., 1998). As noted by Brott and Bogousslavsky (2000):

> Initiation of antihypertensive drug therapy is indicated in patients with stroke who have aortic dissection, acute myocardial infarction, heart failure, acute renal failure, or hypertensive encephalopathy and for patients receiving thrombolytic therapy in whom the systolic pressure is 180 mm Hg or higher or the diastolic pressure is 105 mm Hg or higher. In such patients, the blood pressure should be lowered gradually, and the mean arterial pressure should not be reduced by a total or more than 20 mm Hg.

In such instances, the best parenteral drugs appear to be those that are easily titrated and that have a minimal effect on cerebral blood vessels, such as labetalol or enalaprilat.

Congestive Heart Failure

Hypertension in patients with acute left ventricular failure from systolic dysfunction should be treated with vasodilators that unload the left ventricle. Whereas nitroprusside and nitroglycerin are preferred for immediate relief, ACEIs and angiotensin II–receptor blockers—if they turn out to be as good—will be used more often for more persistent benefit.

Acute Coronary Insufficiency

Acute coronary insufficiency often precipitates additional hypertension. With or without concomitant hypertension, intravenous parenteral vasodilators, mainly nitroprusside and nitroglycerin, have been tested in 11 trials involving 2,170 patients with acute myocardial infarction and have reduced mortality by a highly significant 43% (Lau et al., 1992).

Acute Aortic Dissection

Hypertension is frequently present in patients who experience an acute aortic dissection. The usual patient is an elderly man with a long history of hypertension who presents with a tearing or ripping severe chest pain of rapid onset, mediastinal widening, and pulse and BP differentials between the two arms (von Kodolitsch et al., 2000). However, it can also occur in young patients with severe hypertension (Vogt et al., 1999). High levels of circulating smooth-muscle myosin heavy-chain protein may be of diagnostic help (Suzuki et al., 2000). If the event is suspected on clinical grounds, transesophageal echocardiography, computed tomographic scans, or magnetic resonance imaging will usually confirm the diagnosis (Prêtre and Von Segesser, 1997).

As described in Chapter 4, the stresses that damage the vessel wall are related not only to the mean pressure but also to the width of the pulse pressure and the

maximal rate of rise of the pressure (*dp/dt*). Therefore, drugs that diminish *dp/dt*, such as nitroprusside, particularly in combination with a b-blocker, are the best to treat a dissection (Asfoura and Vidt, 1991). Increasingly, dissections of the ascending aorta (type A) are being treated by immediate surgery (Ehrlich et al., 2000) and those of the descending aorta (type B) by endovascular stent grafts (Czermak et al., 2000) or fenestration (Beregi et al., 2000).

Other Specific Circumstances

The management of hypertensive emergencies in a number of special circumstances is considered in other chapters of this book: renal insufficiency, Chapter 9; eclampsia, Chapter 11; pheochromocytoma, Chapter 12; drug abuse, Chapter 15; and, in children and adolescents, Chapter 16.

THERAPY FOR HYPERTENSIVE URGENCIES

Hypertensive urgencies can usually be managed with oral therapy, including many cases of accelerated-malignant hypertension or perioperative or rebound hypertension. This does *not* include the overwhelming majority of patients who are found to have a very high BP but who are asymptomatic and in little danger of rapidly progressive target organ damage. The management of such patients, whose BP is better referred to as *uncontrolled severe* rather than *urgent*, is considered at the end of this chapter.

In particular, patients in a surgical recovery room or a nursing home whose BP is found to be above some arbitrary danger level such as 180/110 mm Hg should not automatically be given sublingual nifedipine or any other antihypertensive drug. This practice has been wide-spread. In a 2-month survey in three hospitals, 3.4% of all patients had been given sublingual nifedipine: 63% of the orders were given over the telephone for arbitrary and asymptomatic BP elevations and 98% with no bedside evaluation (Rehman et al., 1996). One patient had severe hypotension accompanied by an acute myocardial infarction.

Rather than such inappropriate prescribing, the proximate causes for abrupt increases in BP should be identified and managed (e.g., hypoxia, pain, or volume overload in the post-operative patient; a distended bladder, disturbed sleep, or arthritic pain in the nursing home patient). Only if the BP remains above 180/110 mm Hg after 15 to 30 minutes may there be a need for additional antihypertensive therapy but not for rapid and precipitous reduction of BP as induced by sublingual nifedipine. If such rises in BP are frequent, appropriate increases in long-term therapy may be indicated.

Choice of Oral Agents

Virtually every available antihypertensive drug with a fairly short onset of action has been shown to be effective in patients with uncontrolled, severe hypertension, including some—such as minoxidil—that seem inappropriate. None is clearly better than the rest, and a combination will often be needed for long-term control. Those most widely used are listed in Table 8-6; complete information about them is provided in Chapter 7.

Drug	Class	Dose	Onset	Duration (h)
Captopril (Capoten)	Angiotensin-converting enzyme inhibitor	6.5–50.0 mg	15 min	4–6
Clonidine (Catapres)	Central α-agonist	0.2 mg initially, then 0.1 mg/h, up to 0.8 mg total	0.5–2.0 h	6–8
Furosemide (Lasix)	Diuretic	20–40 mg	0.5–1.0 h	6–8
Labetalol (Normodyne, Trandate)	α- and β-Blocker	100–200 mg	0.5–2.0 h	6–12
Nifedipine (Procardia, Adalat)	Calcium channel blocker	5–10 mg	5–15 min	3–6
Propranolol (Inderal)	β-Blocker	20–40 mg	15–30 min	3–6

TABLE 8-6. *Oral drugs for hypertensive urgencies*

Nifedipine

The rapidly acting formulation of the CCB nifedipine has been widely used for the treatment of hypertensive urgencies (Bertel et al., 1983; Grossman et al., 1996). Liquid nifedipine in a capsule will usually lower BP after a single 5- or 10-mg oral dose (Maharaj and van der Byl, 1992). The drug is effective even more quickly when the capsule is chewed and the contents are swallowed than when it is squirted under the tongue (van Harten et al., 1987).

As might be expected with any drug that induces such a significant and rapid fall in BP, with no way to titrate or overcome the response, occasional symptomatic hypotension can occur, resulting in severe cerebral or cardiac ischemia (Grossman et al., 1996). Grossman et al. (1996) therefore recommended that the use of short-acting nifedipine be abandoned. However, if taken in the unbroken capsule, it seems no more likely to cause a precipitous fall in BP than other short-acting agents (e.g., captopril). Certainly, there is no place for such short-acting formulations in the chronic treatment of hypertension, but if the BP needs to be lowered over a few hours, short-acting nifedipine is an acceptable choice. Other slower and, therefore, possibly safer oral CCB formulations such as short-acting diltiazem, felodipine, or verapamil can be used (Damasceno et al., 1997).

Captopril

Captopril is the fastest acting of the oral ACEIs now available, and it can also be used sublingually in patients who cannot swallow (Angeli et al., 1991). As noted earlier in this chapter, an ACEI may be particularly attractive because it shifts the entire curve of cerebral autoregulation to the left, so CBF should be well maintained as the systemic BP falls (Barry, 1989).

Abrupt and marked first-dose hypotension after an ACEI has been rarely observed, usually in patients with high renin status (Postma et al., 1992). Caution is advised in patients who have significant renal insufficiency or who are volume-depleted. Despite the small potential for hypotension, oral captopril may be the safest of nonparenteral agents for urgent hypertension. Moreover, if renovascular hypertension needs to be looked for, a blood sample for plasma renin activity can be obtained just before and 1 hour after the 25-mg dose as a reasonably accurate screening test (see Chapter 10).

Clonidine

Clonidine, a central a-agonist, has been widely used in repeated hourly doses to reduce very high BP safely and effectively. It works more slowly than nifedipine but eventually brings the pressure down about as well and more safely (Jaker et al., 1989).

Significant sedation is the major side effect that contraindicates its use in patients with central nervous system involvement. Because it has a greater proclivity than other drugs to cause rebound hypertension if it is suddenly discontinued, it should not be used by patients who have demonstrated poor compliance with therapy. Despite its past popularity, clonidine seems to be a most unattractive drug for such patients.

Labetalol

The a- and b-blocker labetalol has been given in hourly oral doses ranging from 100 to 200 mg. It has reduced elevated pressures as effectively as repeated doses of oral nifedipine; it works somewhat more slowly and, perhaps, more safely (McDonald et al., 1993).

Diuretics

Diuretics, specifically furosemide or bumetanide, often are needed in patients with hypertensive urgencies, both to lower the BP by getting rid of excess volume and to

prevent the loss of potency from other antihypertensives because of their tendency to cause fluid retention. However, volume depletion may be over-done, particularly in patients who start off with a shrunken fluid volume. Thereby renin secretion may be further increased, producing more intensive vasoconstriction and worsening the hypertension.

Management after Acute Therapy

Continued Evaluation for Identifiable Causes

After the patient is out of danger, a careful search should continue for possible identifiable causes, as delineated earlier in this chapter in the section Evaluation. Identifiable causes, in particular renovascular hypertension, are much more likely in patients with severe hypertension.

Chronic Therapy

Most patients will likely require multiple drug therapy. All of the guidelines delineated in Chapter 7 should be followed to ensure adherence to effective therapy.

UNCONTROLLED SEVERE HYPERTENSION

Management

Most patients who are diagnosed and treated as a hypertensive urgency are not in the immediate danger of uncontrolled hypertension that this diagnosis connotes. They are simply patients with very high BP, often as a consequence of discontinuing prior therapy, but in no distress. They may need nothing more than observation for a few minutes for the BP to come down to levels not deemed to require immediate therapy (Lima et al., 1997). As shown in Figure 8-5, if BP remains higher than 180/120 mm Hg, such patients should be started on appropriate oral therapy, perhaps with a combination of medications; if prior therapy was successful and well tolerated, that regimen could be restarted; if prior therapy was unsuccessful or not well tolerated, appropriate changes should be made. If this is the first instance of severe hypertension, a workup for possible identifiable causes should be performed.

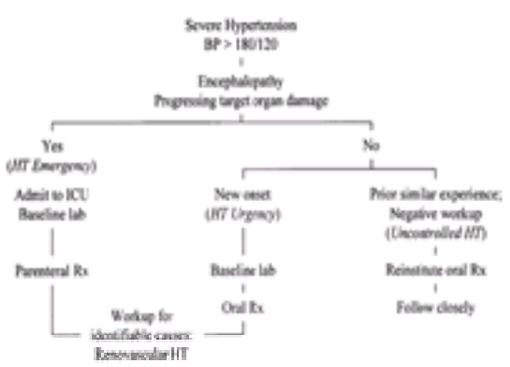

FIG. 8-5. Pathways for management of patients with severe hypertension, defined as blood pressure (BP) in excess of 180/120 mm Hg. HT, hypertension; ICU, intensive care unit; Rx, therapy.

Choice of Drugs

Logically, shorter-acting formulations of whatever class of drug that seems appropriate for long-term therapy should be used (Table 8-6). Thus, if a diuretic and an ACEI are to be used chronically, an oral dose of furosemide and captopril could be given acutely.

Although most such patients could be safely started on one or more oral drugs and sent home to return in 24 or 48 hours for confirmation of their responsiveness, it seems preferable to observe them for a few hours after administration of antihypertensive therapy to ensure responsiveness. Once BP is down to a safer level, chronic therapy should be started.

We will now leave the realm of primary hypertension and look in depth at the various secondary forms of hypertension, starting with the most common: renal parenchymal disease.

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9
Renal Parenchymal Hypertension

RELATIONSHIP BETWEEN THE KIDNEYS AND HYPERTENSION

The kidney is important in most forms of hypertension. As described in Chapter 3, a defect in renal function is almost certainly involved in the pathogenesis of primary hypertension, and renal damage often develops in the course of primary hypertension. Therefore, the kidney is both the victim and the culprit. Clinically, there is often a vicious circle: Hypertension causes renal damage, which causes more hypertension.

As noted in Chapter 1, chronic renal disease (CRD) is the most common of the identifiable causes of hypertension, present in 2% to 5% of all hypertensives. In the United States, an estimated 3% of the population—5.6 million people—have elevated serum creatinine levels, 70% of whom are hypertensive (Coresh et al., 2001). At the same time, hypertension is second only to diabetes among the causes of end-stage renal disease (ESRD) (U.S. Renal Data System, 2000).

For multiple reasons, CRD and ESRD will become even more common and use an increasing share of health care expenditures. For the U.S. population, projections to the year 2010 indicate almost a doubling of the figures in 2000 (Collins et al., 2000). There will be over 650,000 patients with ESRD, 520,000 on dialysis, 180,000 with kidney transplants, all at a total cost of more than $28 billion. The reasons for these marked increases in renal disease are multiple, including:

- The increasing age of the population (Clase and Kiberd, 2000).
- The progressive rise in obesity and consequent diabetes mellitus (Stengel et al., 2000).
- The growing proportion of Hispanics and blacks, both more susceptible to renal disease (Xue et al., 2000). The lifetime cumulative risk for ESRD in black women in 2001 is estimated to be 9.7% (Kiberd and Clase, 2000).

Although these figures for the United States may be higher than those elsewhere (Maisonneuve et al., 2000), they will surely pose an increased burden as the numbers of renal patients expand, particularly because these patients' risk for cardiovascular disease (CVD) is more than fivefold increased as compared to that of the general population (Longenecker et al., 2000; Ruilope, 2001).

As noted in Chapter 4, hypertension may be less common a cause for progressive renal disease than was previously thought (Frassinetti Fernandes et al., 2000). However, this lesser contribution to ESRD is overbalanced by the frequency of microalbuminuria and the recognition that its presence may connote a greater risk for CVD than either hypertension or hypercholesterolemia (Hillege et al., 2000). Moreover, hypertension, if not as often the primary cause for progressive renal disease, almost always develops in the course of all other causes and speeds their progression (Ruggenenti et al., 2000b).

As bad as this scenario looks, there is a countervailing, brighter aspect: The control of hypertension undoubtedly can slow, if not stop, the progression of renal damage (Marcantoni et al., 2000). Therefore, the identification and control of hypertension is the most practical way to slow the onslaught of renal disease.

We will now examine specific varieties of renal disease and how they relate to hypertension, starting from one extreme (the total absence of renal tissue) and going to the other (the presence of only unilateral renal involvement). Renovascular hypertension induced by renal artery stenosis is covered in the next chapter. It should always be kept in mind as a potentially curable form of ESRD (Textor and Wilcox, 2000).

HYPERTENSION IN THE ABSENCE OF FUNCTIONING KIDNEYS

Using peritoneal dialysis and hemodialysis, it is possible to keep people with nonfunctioning renal tissue alive for years. Because they are unable to excrete sodium and water, their hypertension likely develops in the pattern shown in Figure 9-1: an increase in fluid volume that leads to a rise in cardiac output, followed by a subsequent conversion to an increased peripheral resistance, presumably through whole-body autoregulation (Coleman et al., 1970). Other mechanisms are likely involved, including the absence of vasodepressors of renal origin (described in Chapter 3) and mediators of oxidative stress (Kitiyakara et al., 2000). As in patients with ESRD, the accumulation of endogenous inhibitors of nitric oxide synthase may inhibit the vasodilation normally provided by nitric oxide and thereby contribute to the hypertension (Morris et al., 2000). Elevated plasma endothelin-1 levels may also be involved (Vajo et al., 1996).

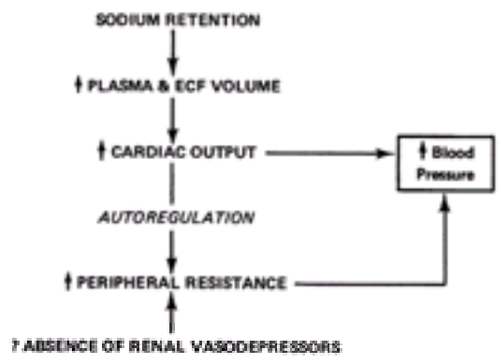

FIG. 9-1. Probable mechanism for hypertension in the anephric state. ECF, extracellular fluid.

A very rare patient with renal failure and severe hypertension unresponsive to volume control during hemodialysis or drug therapy may need bilateral nephrectomy before a functioning homotransplant is possible (Nuutinen et al., 2000). The availability of dialysis and more effective antihypertensive drugs, however, has diminished the need for this drastic step.

BLOOD PRESSURE IN CHRONIC DIALYSIS PATIENTS

Hypertension is common in patients entering dialysis and is a risk for premature mortality, mostly due to CVD (Mazzuchi et al., 2000). In a few patients with severe hypertension who have rapidly progressed to ESRD, aggressive antihy- pertensive therapy results in return of enough renal function to allow withdrawal from dialysis (James et al., 1995).

Despite the obvious connection between persistent hypertension and poor outcome, the majority of chronic dialysis patients, in the United States (Rahman et al., 2000) and elsewhere (Grekas et al., 2000; Merkus et al., 2000), remain hypertensive—in spite of widespread use of various antihypertensive medications. As will be noted, the current inadequacy of blood pressure (BP) control almost certainly reflects either the inability to control or inattention to the presence of volume overload (Scribner, 1999).

Variations of Blood Pressure

The BP of patients on chronic dialysis varies considerably with the timing of dialysis. Ambulatory BP monitoring reveals a frequent white-coat effect before dialysis, higher readings on the day after dialysis, and a blunting of nocturnal dipping (Mitra et al., 1999). The absence of a nocturnal fall in BP, although it is poorly reproducible (Peixoto et al., 2000), is a potent indicator of mortality (Amar et al., 2000). Mitra et al. (1999) recommend the 20-minute postdialysis reading as most representative of interdialytic BP.

Management of Hypertension

As little as a 2.5-kg weight gain between dialysis sessions is associated with a significant rise in BP (Aravind and Raja, 2000), and there is a significant correlation between BP and interdialytic weight gain in hypertensive patients (Rahman et al., 2000). Despite the use of multiple antihypertensive drugs, control of BP may not be possible if dry weight is not achieved by ultrafiltration and dietary sodium restriction (Scribner, 1999). As Shaldon (2000) stated: “Perhaps if the value of a salt-restricted intake was rediscovered in the USA, control of hypertension in dialysis patients would improve.”

The critical importance of obtaining control of hypertension by achieving a normal extracellular fluid volume (ECV) by longer periods of dialysis has been emphasized by Scribner (1999). He notes the report of Innes et al. (1999) showing higher mortality rates in the hemodialysis center in Nottingham, U.K. as compared to the rates in Tassin, France:

> After careful analysis of all relevant risk factors such as age and comorbidity, the authors conclude that the main identifiable factor, which could explain this difference in survival, is a marked difference in blood pressure among the patients from each unit. In Nottingham, most patients had chronic hypertension: in Tassin, which uses the drug free dry weight method of BP control (Charra et al., 1998), BP of almost all their patients was in the low normal range. . . . Normotensive haemodialysis patients in dry weight have a time averaged ECV that is similar in size to that of primitive tribes who ingest a very low sodium diet or patients with essential hypertension that have been successfully treated by the rice/fruit diet. In the case of dialysis patients, this low normal level of ECV is maintained by the powerful tool, ultrafiltration, which if properly used along with moderate dietary sodium restriction is the only proven method of controlling BP in the haemodialysis population (Scribner, 1999).

Daily hemodialysis in the home has been shown to minimize wide swings in ECV and bring BP under control using the Tassin dry-weight regimen even with a slightly more liberal dietary sodium intake (Pierratos et al., 1998). The better BP control usually achieved with hemodialysis than with peritoneal dialysis is probably related to the better control of body fluid volume (Velasquez et al., 1997; Rocco et al., 2001). Long, slow hemodialysis usually provides good BP control without antihypertensive drugs (McGregor et al., 1999).

An additional lowering of BP has been noted by the use of biocompatible dialysis membranes, which reduce the levels of inhibitors of nitric oxide synthase (Schröder et al., 2001).

Hypotension

Hypotension during dialysis can arise from multiple causes (Table 9-1) and may be a major problem, especially in the patient who is debilitated (Port et al., 1999). In such cases, the ECV becomes even more difficult to control, and a constant state of ECV excess may be necessary to avoid severe episodes of hypotension during dialysis. Normotension or less severe hypertension in a patient who is starting dialysis is a bad prognostic sign (Murphy et al., 2000) and is usually associated with complicating illnesses such as heart failure, severe uremic malnutrition, or debility due to advanced age.

Excessive ultrafiltration
Decrease of plasma osmolality
Dialysate problems: temperature, bioincompatibility
Hyperinsulinemia from dialysate-induced hyperglycemia
Reflex sympathetic inhibition
Autonomic neuropathy
Bleeding
Electrolyte abnormalities (hypokalemia, hyperkalemia, hypocalcemia)
Sepsis
Heart disease (ischemia, arrhythmias, pericardial effusion with cardiac tamponade)
Restoration of nitric oxide by removal of endogenous inhibitors

TABLE 9-1. *Causes of dialysis-related hypotension*

Other Risk Factors

In view of the high level of cardiovascular risk in most of these patients, full attention to other risk factors should be provided, even though they do not fully explain the

high prevalence of coronary disease (Cheung et al., 2000). An impressive reduction in the incidence of CVD was obtained by supplementation of 800 IU per day of vitamin E in a randomized, controlled trial of 196 dialysis patients with preexisting CVD (Boaz et al., 2000). However, as Pereira (2000) emphasizes, the best way to improve dialysis outcomes is to optimize pre-ESRD care by appropriate interventions against all the known risk factors before the patient begins dialysis.

HYPERTENSION AFTER KIDNEY TRANSPLANTATION

As more patients are receiving renal transplants and living longer thereafter, hypertension has been recognized as a major complication, one that may, if uncontrolled, quickly destroy the transplant or add to the risk of accelerated atherosclerosis (Li et al., 2000). The majority of transplant recipients are hypertensive, and the higher the level of BP at 1 year after transplantation, the lower is the rate of allograft survival (Mange et al., 2000).

A number of associations between BP in either donor or recipient and posttransplantation hypertension have been noted:

- Hypertension is more likely after transplantation in patients who were hypertensive before receiving the transplant: Posttransplantation hypertension was noted in 14% of patients who had been normotensive but in 60% of those who had been hypertensive (Rao et al., 1978).
- Preexisting hypertension or diabetes in the donor kidney reduces graft survival to a moderate degree (Ojo et al., 2000).
- In normotensive recipients without a family history of hypertension, donor kidneys from normotensives with a positive family history transmit more hypertension and a greater rise in BP during acute rejections (Guidi et al., 1998).
- On the other hand, receipt of a kidney from a normotensive donor may relieve primary hypertension that preceded (and presumably caused) the renal failure (Curtis et al., 1983).

Causes and Management

Table 9-2 lists a number of causes of posttransplantation hypertension beyond persistence of primary hypertension.

Immunosuppressive therapy
Steroids
Cyclosporine, tacrolimus
Allograft failure
Chronic rejection
Recurrent disease
Potentially surgically remediable causes
Allograft renal artery stenosis
Native kidneys
Volume expansion
Erythrocytosis
Sodium retention
Speculative cause
Recurrent essential hypertension
As a primary cause of end-stage renal disease
From a hypertensive or prehypertensive donor
Other pressor mechanisms including:
Endothelin
Transforming growth factor–β

TABLE 9-2. *Causes of posttransplantation hypertension*

Cyclosporine and Tacrolimus

As described in Chapter 15, cyclosporine and tacrolimus can cause both nephrotoxicity and hypertension, and the two are often interrelated. As described further in Chapter 15, a calcium channel blocker (CCB) is the most effective antihypertensive (Rahn et al., 1999). Diuretics and angiotensin-converting enzyme inhibitors (ACEIs) may also be needed.

Posttransplantation Renal Artery Stenosis

Renal artery stenosis, often at the suture line, is found in approximately 2% to 4% of patients with posttransplantation hypertension and may be suspected by appearance of a bruit. The diagnosis should be suspected if hypertension suddenly appears or rapidly progresses or if allograft function deteriorates after an ACEI is begun. Duplex sonography may visualize the stenosis. Success has been reported with both percutaneous angioplasty and surgical repair (Rengel et al., 1998) (see Chapter 10).

Native Kidney Hypertension

If graft stenosis is excluded and the allograft is functioning well, the native kidneys may be responsible for the hypertension. If so, plasma renin activity may be increased (Bresticker et al., 1991) and ACEIs may prove useful. If the hypertension persists despite aggressive medical therapy, the native kidneys may have to be removed (Fricke et al., 1998).

Medical Therapy

If there is no correctable cause, antihypertensive therapy is needed. ACEIs and angiotensin II– receptor blockers (ARBs) usually work well (Stigant et al., 2000). Their effects may involve relief of erythrocytosis (Montanaro et al., 2000). CCBs (Rump et al., 2000) and a-blockers (Martínez-Castelao et al., 1998) have also been effective. b-Blockers are indicated for those with coronary disease (Suwelack et al., 2000). The BP should be lowered to below 130/80 mm Hg (Klassen, 2000) and attention given to other risk factors such as dyslipidemia (Peschke et al., 1999) and control of diabetes (Kasiske et al., 2000).

HYPERTENSION WITH CHRONIC RENAL DISEASE

Patients may start at either end of the spectrum: hypertension without overt renal damage on the one end and severe renal insufficiency without hypertension on the other. Eventually, however, both groups move toward the middle—renal insufficiency with hypertension—so that hypertension is found in approximately 85% of patients with CRD of diverse causes and is closely related to the progression of nephropathy (Ruggenenti et al., 2000b). Renal insufficiency as a consequence of primary hypertension is described in Chapter 4. This section examines the development of hypertension as a secondary process in the presence of primary renal disease. Diabetic nephropathy is covered later in this chapter.

Patients whose underlying problem is bilateral renovascular disease may present with refractory hypertension and renal insufficiency (Textor and Wilcox, 2000). The recognition of the renovascular etiology of these patients' condition is critical, because revascularization may relieve their hypertension and improve their renal function. More about this important group of patients with ischemic nephropathy is provided in the next chapter.

Prevalence

Hypertension is common in patients with overt renal insufficiency, as defined by a glomerular filtration rate (GFR) of less than 50 mL per minute or a serum creatinine higher than 1.5 mg per dL. Overall, the prevalence of hypertension is inversely correlated to the GFR, but the prevalence varies considerably in various forms of renal disease and even within the category of chronic glomerulonephritis, being most common with focal and segmental sclerosis (Brown and Whitworth, 1992).

In patients with CRD, BP may not dip during sleep, adding further to the cardiovascular and renal burden (Schömig et al., 2000).

Significance

Hypertension is associated with a more rapid progression of renal damage, regardless of the underlying renal disease. This was demonstrated in the large

Modification of Diet in Renal Disease Study, involving 585 patients with a GFR between 25 and 55 mL per minute and 255 patients with a GFR between 13 and 24 mL per minute (Lazarus et al., 1997). Among those with proteinuria of more than 1 g per day at baseline, the rate of decline in GFR was significantly less over a mean follow-up of 2.2 years in both groups whose BPs remained an average of 5 mm Hg lower as a result of more intensive therapy.

As noted in Chapter 4, blacks develop ESRD at a higher rate, almost fourfold higher than whites in the large Multiple Risk Factor Intervention Trial population (Klag et al., 1997). Most of their higher risk is derived from their higher prevalence of hypertension (Tarver-Carr, 2000). Together, these are major contributors to the excess mortality of U.S. blacks (Young and Gaston, 2000).

In addition to its role in advancing renal damage, hypertension may be the most common risk factor for the many-fold increased risk for CVD seen in patients with renal insufficiency, acting in concert with other risk factors (Baigent et al., 2000).

Mechanisms

The mechanism by which hypertension leads to progressive renal damage most likely involves glomerular hypertension, as championed by Brenner and co-workers (Anderson and Brenner, 1989) (Fig. 9-2). Their hypothesis starts with any of a number of factors that increase glomerular capillary plasma flow rate or hydraulic pressure.

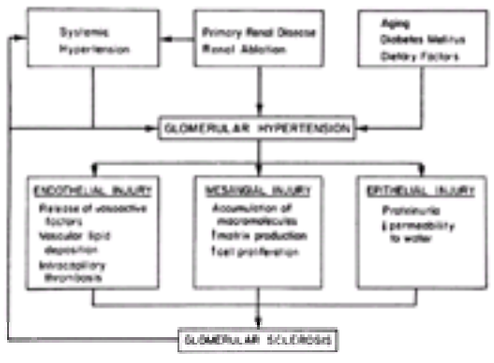

FIG. 9-2. Pivotal role in glomerular hypertension in the initiation and progression of structural injury. (Reprinted from Anderson S, Brenner BM. Progressive renal disease: a disorder of adaptation. QJM 1989;70:185–189, with permission.)

As shown in the upper left of Figure 9-2, systemic hypertension is one of these factors. The high systemic BP may be transmitted into the glomerulus because afferent arteriolar resistance fails to increase adequately (Tolins and Raij, 1991). The higher pressure or flow rate (or both), in turn, damages glomerular cells and leads to progressive sclerosis, setting off a vicious cycle (Zatz, 1996).

The degree of proteinuria, shown in Figure 9-2 to reflect glomerular epithelial injury, serves as a strong predictor of the rate of progression to ESRD. Even when antihypertensive therapy was given to keep the diastolic BP lower than 90, more than one-third of nondiabetic patients with chronic nephropathies who had 24-hour urinary protein levels in the highest tertile (urinary protein, >3.76 g per day) had significant progression over an average 23-month follow-up, whereas only 1 of 67 in the lowest tertile (urine protein, <1.92 g per day) progressed (Ruggenenti et al., 1996). These authors, among others, have emphasized a direct role of protein overloading of the tubules in progressive renal damage (Remuzzi et al., 1997; Walls, 2001).

Contributing Factors

A number of factors are likely involved in the vicious cycle of hypertension and progressive renal damage (Ritz et al., 2000). These include:

- Sodium retention (Cowley et al., 1994).
- Inappropriate activation of the reninangiotensin-aldosterone system (Cao et al., 2000). In particular, aldosterone may be a primary promoter of progressive renal damage (Epstein, 2001).
- Sympathetic nervous overactivity (Campese, 2000).
- Decreased nitric oxide–mediated vasodilation (Schmidt and Baylis, 2000). This, in turn, may reflect inhibition of NO synthesis by retained, endogenous, asymmetric dimethylarginine (Vallance et al., 1992).
- Contributions from multiple turned-on hormonal mechanisms, including cortisol (Ferrari and Krozowski, 2000), insulin resistance (Stenvinkel et al., 1995), parathyroid hormone (Rostaing et al., 1997), or mediators of oxidative stress (Kitiyakara et al., 2000).
- Exogenous erythropoietin (Vaziri et al., 2001).

Renin-Dependent Hypertension

A small number of patients with CRD and severe hypertension may have a highly activated renin-angiotensin system either from bilateral renal artery stenosis or, more likely, from diffuse intrarenal ischemia.

Sickle-Cell Nephropathy

Among 381 patients with sickle-cell disease, 26% had proteinuria and 7% had elevated serum creatinine levels (Falk et al., 1992). Proteinuria decreased during therapy with an ACEI, sup-porting glomerular capillary hypertension as a mechanism for the nephropathy.

Management

Some patients are initially seen only at the end stage of renal disease, at which time all that can be done is to enter them into dialysis with the hope for transplantation. As noted, the total number of ESRD patients on chronic dialysis in the United States will likely reach 650,000 by the year 2010 (Collins et al., 2000), consuming a significant amount of money that likely could be far more effectively spent on prevention, as the two most common causes of ESRD—hypertensive nephrosclerosis and diabetic nephropathy—are largely preventable.

With lesser degrees of renal insufficiency, the goal is to slow its progress by interrupting the vicious cycle shown in Figure 9-2. As of now, the only means known to be effective are control of hypertension and, according to some, decreasing the intake of dietary protein; however, control of hyperlipidemia (Fried et al., 2001), reduction in the degree of proteinuria, and restriction of phosphorus intake may also be helpful (Ritz et al., 2000).

There is increasingly strong evidence for the protective effect of antihypertensive therapy with additional benefits of ACEIs, which go beyond the reduction in BP and proteinuria they provide (Hunsicker et al., 2000; Ruggenenti et al., 2001). The optimal level of BP and proteinuria is likely much lower than is currently considered. In an analysis of 1,850 patients with nondiabetic renal disease from 11 randomized, controlled trials, the lowest risk of adverse outcome was at a systolic BP of 110 mm Hg and with minimal to no proteinuria (Jafar et al., 2000).

With antihypertensive therapy, transient falls in renal blood flow and GFR may accompany successful reduction of the BP. In fact, in patients with a serum creatinine in excess of 1.4 mg per dL given an ACEI or a b-blocker, acute increases in serum creatinine of up to 30% were associated with *better* long-term preservation of renal function (Apperloo et al., 1997). Unless there is reason to believe that plasma volume is contracted too much or that there is drug-related nephrotoxicity, the best course is to proceed with control of the hypertension despite a modest rise in the serum creatinine. In the long run, renal function is best preserved by tight control of the hypertension (Jafar et al., 2000). Fortunately, the desired control of hypertension can usually be obtained, as shown among the patients with renal impairment

enrolled in the Hypertension Optimal Treatment study (Ruilope et al., 2001).

The publications by Bennett and co-workers (Olyaei et al., 1999) provide the best data about the dosage of antihypertensive and other drugs in patients with varying degrees of CRD (Table 9-3).

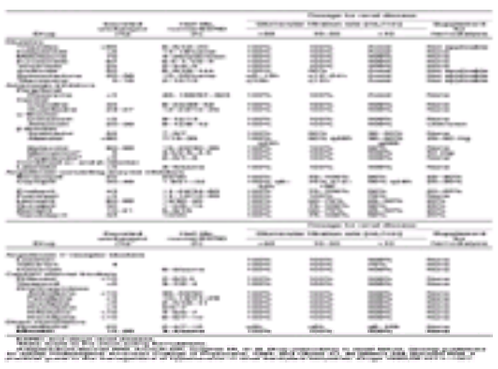

TABLE 9-3. *Antihypertensive drug dosage in chronic renal disease*

Sodium Restriction

Patients with CRD may have a narrow range of sodium excretory capacity: If their dietary salt is markedly restricted, they may not be able to conserve sodium and will become volume-depleted; if given modest salt loads, they may be unable to excrete enough sodium to prevent volume expansion and hypertension. A small number have severe salt-losing nephropathy, but that condition is seldom associated with hypertension (Uribarri et al., 1983).

Sodium restriction to the range of 1 to 2 g per day (sodium, 44 to 88 mEq per day) is both feasible and necessary to control the hypertension in these patients. The importance of dietary sodium restriction in proteinuric patients goes beyond its ability to enhance the antihypertensive effect of all drugs (save CCBs). If dietary sodium intake is as high as 200 mmol per day, the antiproteinuric efficacy of both ACEIs (Heeg et al., 1989) and nondihydropyridine CCBs (Bakris and Smith, 1996) may be inhibited, presumably reflecting hyperfiltration induced by the high sodium intake (Mallamaci et al., 1996).

Diuretics

All diuretics, save spironolactone, must gain entry to the tubular fluid and have access to the luminal side of the nephron to work. They reach the tubular fluid by secretion across the proximal tubule by way of organic acid or base secretory pathways. Patients with CRD thus are resistant to acidic diuretics such as thiazides and the loop diuretics, both because of their reduced renal blood flow and because of the accumulation of organic acid end products of metabolism that compete for the secretory pump. To effect diuresis, enough of the diuretic must be given to deliver adequate amounts of the agent to the tubular sites of action. This translates into a "sequential doubling of single doses until a ceiling dose is reached" (Brater, 1988). Once the ceiling dose is reached, that dose should be given as often as needed as a maintenance dose.

As Brater (1988) points out, thiazides would probably work in many CRD patients if given in high enough doses; "however, such a strategy is still not worth pursuing [because of] the low intrinsic efficacy of these drugs compared to loop diuretics." Most clinicians do not try thiazides if the serum creatinine level is higher than 2.0 mg per dL. On the other hand, in severely resistant patients, combining a loop diuretic with a thiazide may effect a response when neither is effective alone (Knauf and Mutschler, 1995).

In addition, metolazone may work as well as loop diuretics, with the added benefit of providing a full 24-hour effect with once-a-day dosing (Bennett and Porter, 1973).

Caution should be exercised to avoid excessive diuresis with such potent diuretics, on the one hand, and interference with diuretic action by nonsteroidal antiinflammatory drugs (NSAIDs), on the other. The recently introduced COX-1– sparing NSAIDs are likely just as nephrotoxic, however, and interfere as much with sodium excretion as do the older NSAIDs (Perazella and Eras, 2000). Spironolactone, triamterene, and amiloride should be avoided in most patients with severe CRD, because they may induce hyperkalemia On the other hand, the favorable effects of low doses of spironolactone in heart failure patients (Zannad et al., 2000) and the likely pathogenetic role of aldosterone in renal injury (Epstein, 2001) may lead to a greater use of aldosterone antagonists in CRD patients in the future.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II–Receptor Blockers

In keeping with the hypothesis of Brenner and coworkers (Taal and Brenner, 2000), ACEIs have been shown to provide better control of glomerular hypertension and better preservation of renal function than other drugs that lower the BP equally well (Jafar et al., 2001;,Ruggenenti et al., 2000a, and Ruggenenti et al., 2001,). The observation is in keeping with a greater degree of efferent arteriolar vasodilation provided by blockade of intrarenal angiotensin II. By relieving this efferent vasoconstriction to a greater degree than they reduce afferent resistance, ACEIs should reduce pressure within the glomeruli, thereby providing protection against progressive sclerosis (Tolins and Raij, 1991) (Fig. 9-3). In addition to their unique hemodynamic benefits, ACEIs (and ARBs) also block other angiotensin II–mediated adverse renal effects (Palmer, 2001).

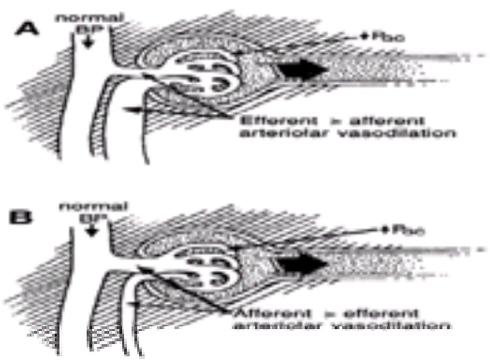

FIG. 9-3. Effect of antihypertensive treatment on glomerular hemodynamics as determined by micropuncture studies in rats. **A:** Angiotensinconverting enzyme inhibition results in normalization of blood pressure (BP) associated with vasodilatation, predominantly of the efferent arteriole, resulting in normalization of intraglomerular capillary pressure (P_{GC}). **B:** With calcium channel blockers, reduction of BP is offset by afferent arteriolar vasodilatation, and therefore, P_{GC} remains elevated. (Reprinted from Tolins JP, Raij L. Antihypertensive therapy and the progression of chronic renal disease. Are there renoprotective drugs? *Semin Nephrol* 1991;11: 538–548, with permission.)

The best currently available evidence for the special renoprotective benefits of ACEIs comes from the Ramipril Efficacy in Nephropathy (REIN) study, in which 352 patients with chronic nondiabetic nephropathies associated with proteinuria of 1 g per day or more and GFR of 20 to 70 mL per minute per 1.73 m^2 were followed prospectively for a median of 4 years with either ramipril or placebo plus other antihypertensive agents (but not ACEIs) (Ruggenenti et al., 2000a). A renoprotective effect of ramipril was seen both in normotensive and hypertensive subjects, but those who were hypertensive with proteinuria greater than 2 g per day, primary glomerular disease, or nephrosclerosis gained the most. The protection from GFR decline correlated with reduction in proteinuria. The rate of GFR decline was relatively slow and virtually unaffected by ramipril treatment in patients with proteinuria of less than 2 g per day. As the authors state, "These findings do not

necessarily mean that ACEIs do not benefit patients with less severe proteinuria, but rather imply that a very long follow-up is needed to definitely show a significant renoprotective effect in slowly progressing nephropathies" (Ruggenenti et al., 2000a).

Subsequently, the REIN study investigators provided additional information about the roles of gender and ACE gene polymorphism in the response to ACEI therapy (Ruggenenti et al., 2000c). They found that ramipril was much more effective in women than in men, regardless of their ACE polymorphism. In men, only those with the DD genotype benefited.

As Hebert (2000) notes, the DD genotype has been found to be associated with a greater risk of progression of renal disease in insulin-dependent diabetes mellitus patients than has the II or ID genotypes (Vleming et al., 1999), so that this greater effectiveness of ramipril in those men with the DD genotype is not surprising. However, the total lack of effect in those men with the II and ID genotypes is surprising.

Hebert (2000) notes other issues that were not resolved by the REIN study because of its design—namely the fixed low doses of ramipril—and the consequent failure to control the systolic BP vigorously. A higher dose of ramipril, 10 mg per day, reduced the risk of CVD in the 980 high-risk patients in the Heart Outcomes Prevention Evaluation who also had mild renal insufficiency, defined as a serum creatinine of 1.4 mg per dL (Mann et al., 2001). This protection was achieved with only a 3–mm Hg average fall in systemic BP from the 139/79 mm Hg baseline level. Thus, higher doses of ACEIs and lower BP could provide even better overall benefits, and these issues should be settled by other large trials now in progress.

Whether ARBs will do as well as ACEIs is not now known. An ARB may not raise serum potassium as much as an ACEI, likely related to a relatively small decrease in plasma aldosterone by the ARB (Bakris et al., 2000a). Some believe that optimal renoprotection may come from the combination of an ACEI and an ARB (Komers and Anderson, 2000). Hopefully, outcome data will settle these issues.

Monitoring of blood chemistries within a few days of starting ACEI or ARB therapy is essential, as a rapid and sustained rise in serum creatinine may occur with unrecognized bilateral renovascular disease, or significant hyperkalemia may develop.

Calcium Channel Blockers

As seen in Figure 9-3, CCBs may dilate afferent arterioles as much or more than efferent arterioles. Because renal autoregulation is already impaired in patients with renal disease, intraglomerular pressure would thereby increase (Palmer, 2001). However, if the CCB lowers systemic BP sufficiently, it will also lower intraglomerular pressure and provide renoprotection. Proteinuria has been used as a surrogate for renoprotection. In most studies, dihydropyridine CCBs do not reduce proteinuria, whereas nondihydropyridine CCBs do (Kloke et al., 1998).

The issue of renoprotection by CCBs was addressed in the initial phases of the REIN study, wherein 63% of patients received a dihydropyridine CCB with or without an ACEI (Ruggenenti et al., 1998). The effects of urinary protein excretion were examined as a function of BP control and whether or not the patient was also taking an ACEI. In patients who achieved a mean arterial pressure (MAP) of 117 or 105 mm Hg, 24-hour urinary protein excretion was greater in patients receiving dihydropyridine CCBs as compared to subjects treated with drugs other than CCBs. In patients with a lower achieved MAP (94 mm Hg), this adverse effect of CCB therapy on urinary protein excretion was no longer present. In contrast to CCB therapy, use of ACEIs was associated with a reduction in urinary protein excretion at a higher level of MAP (117 and 105 mm Hg). However, similar to the CCB group, urinary protein excretion was no different in patients treated with ACEIs as compared to non-ACEI therapy when MAP was 94 mm Hg. In patients with a MAP of 105 mm Hg, use of an ACEI and CCB together resulted in significantly less proteinuria as compared to patients on CCB therapy alone. These data, along with those from the African-American Study of Kidney Disease and Hypertension (Agodoa et al., 2001), demonstrate that in proteinuric patients, monotherapy with CCBs can increase the level of urinary protein excretion. The increase in proteinuria can be prevented by either a greater reduction in systemic BP or concomitant use of an ACEI.

Without additional outcome data available, the prudent course is to use CCBs only as second or third agents after an ACEI in patients with proteinuric nephropathy.

Minoxidil

Those with refractory hypertension and renal insufficiency may be successfully treated with minoxidil (Toto et al., 1995). As noted in Chapter 7, minoxidil is a potent vasodilator and must be given with an adrenergic blocker (usually a b-blocker) to prevent reflex cardiac stimulation and with a loop diuretic to prevent fluid retention. The drug need be given in only a single daily dose.

Restriction of Dietary Protein

A protein-restricted diet has been recommended for predialysis patients (Walser et al., 1999), but its value has not been established in patients with well-controlled hypertension.

DIABETIC NEPHROPATHY

The progressive nephropathy seen with diabetes mellitus is another example of the deleterious effects of intraglomerular hypertension and hyperfiltration (Hostetter, 2001).

Pathology and Clinical Features

As delineated by Kimmelstiel and Wilson (1936) , renal disease occurs among diabetics with a high incidence and with a particular glomerular pathology—nodular intercapillary glomerulosclerosis. The clinical description has been improved very little since their original paper (Kimmelstiel and Wilson, 1936):

> The clinical picture appears . . . to be almost as characteristic as the histological one: the patients are relatively old; hypertension is present, usually of the benign type, and the kidneys frequently show signs of decompensation; there is a history of diabetes, usually of long standing; the presenting symptoms may be those of edema of the nephrotic type, renal decompensation or heart failure; the urine contains large amounts of albumin and there is usually impairment of concentrating power with or without nitrogen retention.

The pathologic specificity of the nodular glomerular lesion for diabetes has been upheld, although diffuse glomerulosclerosis may be just as common (White and Bilous, 2000). Before overt glomerulosclerosis appears, basement membrane thickening, mesangial expansion, and podocyte loss are noted, usually associated with microalbuminuria. The clinical description should be altered to include younger patients who have been diabetic for more than 15 years, to involve hypertension in approximately 50% to 60% of patients, and to almost always be accompanied by retinal capillary microaneurysms. In the absence of retinopathy, nearly 30% of proteinuric type 2 diabetics will have renal disease unrelated to diabetes (Christensen et al., 2000).

Epidemiology and Genetics

Diabetes is now the most common cause of ESRD in the United States and Europe, because type 2 diabetes is becoming more common in concert with obesity, diabetics live longer, and more of those with diabetic ESRD are being enrolled in dialysis-transplantation programs (American Diabetes Association, 2001). Although fewer type 2 diabetics progress to ESRD, because they compose approximately 90% of the diabetic population, they make up the largest proportion of diabetics with ESRD.

Diabetic nephropathy occurs in family clusters (Tarnow et al., 2000b). The presence of the insertion allele of an insertion/deletion polymorphism in the angiotensin-converting enzyme (ACE) gene (ACE/ID) seems to protect against nephropathy and cardiovascular morbidity (Tarnow et al., 2000b). Angiotensinogen gene M235T polymorphism is also more common in those type 1 diabetics who develop nephropathy (Rogus et al., 1998).

Course

Although there are differences between type 1 and type 2 diabetes in the mechanisms and courses of nephropathy, the course of type 2 diabetes will be emphasized,

particularly because such a clear description of its progression has been presented (Nelson et al., 1996).

Nelson et al. (1996) studied renal function every 6 to 12 months over 4 years in 194 Pima Indians who were selected as representative of different stages in the development of diabetic nephropathy: from normal glucose tolerance to overt diabetes; from normal albumin excretion to macroalbuminuria. As shown in Figure 9-4, the major findings generally were as follows: Glomerular hyperfiltration is present from the onset until macroalbuminuriaappears. Thereafter, GFR declines rapidly because of a progressive loss of intrinsic ultrafiltration capacity. Although the rather abrupt fall in GFR that occurs after approximately 15 years was not prevented by control of BP, higher baseline pressures predicted increasing urinary albumin excretion, which in turn mediated a fall in GFR.

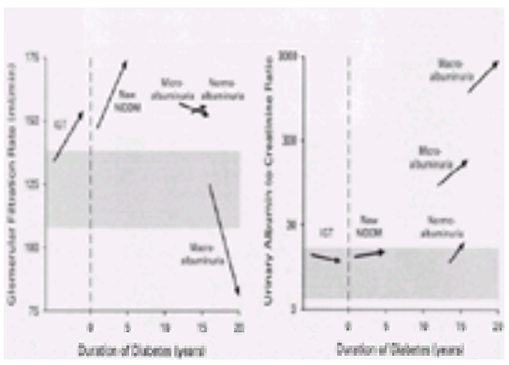

FIG. 9-4. Changes in the mean glomerular filtration rate and median urinary albumin (mg/L) to creatinine (g/L) ratio from baseline to the end of follow-up in subjects with impaired glucose tolerance (IGT), newly diagnosed non–insulin-dependent diabetes mellitus (New NIDDM), NIDDM and normal urinary albumin excretion (normoalbuminuria), NIDDM and microalbuminuria, and NIDDM and macroalbuminuria. Arrows connect the value of the baseline examination with the value at the end of follow-up; dashed lines indicate the time of diagnosis; shaded areas indicate the twenty-fifth and seventy-fifth percentiles of values in subjects with normal glucose tolerance. (Reprinted from Nelson RG, Bennet PH, Beck GH, et al. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1996;334:1636–1642, with permission.)

Mechanisms1

Both metabolic and hemodynamic factors lead to nephropathy (Cooper, 1998) (Fig. 9-5). Cytokines, in particular transforming growth factor–b $_1$(TGF-b$_1$), seem to be the key players in the initiation and progression of nephropathy (Phillips, 2000). Part of the protective effect of ACEIs may involve their inhibition of TGF-b $_1$expression and matrix accumulation.

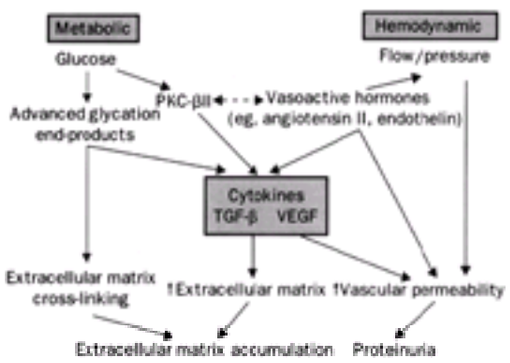

FIG. 9-5. Schema outlining potential interactions between metabolic and hemodynamic factors in the pathogenesis of diabetic nephropathy. PKC, protein kinase C; TGFb, transforming growth factor–b; VEGF, vascular endothelial growth factor. (Reprinted from Cooper ME. Pathogenesis, prevention, and treatment of diabetic nephropathy. *Lancet* 1998;352:213–219, with permission.)

The critical role of glomerular hypertension has been strongly supported by the ability of antihypertensive therapy to prevent the progression of nephropathy (Hovind et al., 2001). In addition to multiple animal studies, the role is supported by the observation that nodular glomerulosclerosis developed in only the nonobstructed kidney of a diabetic patient with unilateral renal artery stenosis (Berkman and Rifkin, 1973). Moreover, normal kidneys trans-planted into diabetic patients develop typical diabetic lesions (Mauer et al., 1983), denying an essential role for genetic factors.

Albuminuria

Microalbuminuria is the usual earliest manifestation of nephropathy. The presence of an even minimally elevated albumin-creatinine ratio in morning first-voided samples beyond 30 µg/mg creatinine is an early indicator of the risk of nephropathy (Schultz et al., 2000).

In addition to its role in nephropathy, proteinuria was associated with a two- to threefold increase in the risk for cardiovascular mortality over a 12-year follow-up in type 2 diabetics as compared to those with normoalbuminuria (Valmadrid et al., 2000).

Hypertension

As reviewed by Mogensen (1995), the associations between hypertension and both increasing albuminuria and falling GFR have been recognized for more than 30 years and repeatedly con-firmed. As nephropathy progresses, the normal dipping of BP during sleep is blunted (Nakano et al., 1996), perhaps because of ECV expansion (Mulec et al., 1995) or autonomic nervous dysfunction (Weinrauch et al., 1995). As nephropathy develops, the prevalence of white-coat hypertension falls considerably (Nielsen et al., 1997).

Renin-Angiotensin

The progressive glomerulosclerosis would be expected to knock out the juxtaglomerular cells that secrete renin and, in some diabetics, a state of *hyporeninemic hypoaldosteronism* appears, usually manifested by hyperkalemia (Perez et al., 1977). However, serum total and prorenin levels are often increased before the onset of microalbuminuria, serving as a potential marker for the development of nephropathy (Deinum et al., 1999). In most non–insulin-dependent diabetes mellitus patients with hypertension, the renin system remains normally activated by a low-sodium diet and upright posture but poorly suppressible by a high-sodium diet (Price et al., 1996). These findings suggest autonomy of the intrarenal renin system and set the stage for the major benefits of ACEIs and ARBs in diabetic nephropathy (Price et al., 1999).

Although renal artery stenoses are common in hypertensive type 2 diabetics (Valabhji et al., 2000), there is no evidence for a higher prevalence of renovascular hypertension.

Management

An overall plan for management of diabetic nephropathy has been presented by Ritz and Orth (1999) (Table 9-4).

Achieve glycemic control (glycosylated hemoglobin concentration to normal); avoid hypoglycemia.
Maintain blood pressure in the mid–normal range (125/75 mm Hg), preferably with the use of angiotensin-converting enzyme inhibitors (possibly also angiotensin II–receptor blockers).
Reduce the level of proteinuria (therapeutic goal is a protein concentration of <1 g per day).
Stop smoking.
Restrict dietary protein intake to approximately 0.8 g per kg of body weight per day, preferably by reducing the intake of animal proteins.

TABLE 9-4. *Measures to prevent progression of overt nephropathy in patients with type 2 diabetes*

Glycemic Control

The first step is control of hyperglycemia, shown conclusively to slow the progress of nephropathy in the Diabetes Control and Complications Trial study of 1,441 insulin-dependent diabetes mellitus patients (Diabetes Control and Complications Trial Research Group, 1993) and in less structured studies of non–insulin-dependent diabetes mellitus patients as well (Levin et al., 2000).

Antihypertensive Therapy*

As reviewed by Mogensen (1999), evidence has been available since 1976 that reduction of elevated BP will slow the progression of diabetic nephropathy. The evidence accumulated from multiple subsequent trials has made two certain conclusions: First, the degree of BP reduction needed to protect against progression is much lower than the previously accepted goal of 140/ 90 mm Hg (Hovind et al., 2001) and, second, multiple drugs will usually be needed to achieve the necessary goal.

The recent special consensus report of the National Kidney Foundation Working Group (Bakris et al., 2000b) has nicely summarized this evidence. As seen in Figure 9-6, the rate of nephropathy progression was directly related to the level of BP achieved in these six trials of patients with diabetic nephropathy and the three trials in nondiabetic renal disease. It required on average more than two, sometimes four or more, drugs to achieve the lower targets of therapy.

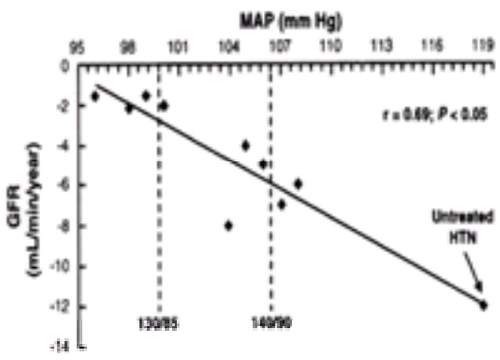

FIG. 9-6. Relationship between achieved blood pressure control and declines in glomerular filtration rate (GFR) in six clinical trials of diabetic and three trials of nondiabetic renal disease. HTN, hyper-tension; MAP, mean arterial pressure. (Reprinted from Bakris GL, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis* 2000;36:646–661, with permission.)

Choices of Drugs

Although the protection provided in the original trials by Mogensen (1976) and Parving et al. (1983) used diuretics, b-blockers, and direct vasodilators—the major drugs available in the 1970s—more recent trials have almost all used ACEIs or ARBs as the primary drug (ACE Inhibitors in Diabetic Nephropathy Trialists Group, 2001). As reviewed earlier in this chapter, ACEIs and ARBs theoretically should reduce intraglomerular pressure better than do other drugs and, practically, they do. The evidence, starting with overt nephropathy in hypertensive type 1 diabetics, has now progressed to encompass type 2 diabetics who are normotensive either with microalbuminuria (Lacourcière et al., 2000) or with normoalbuminuria (Ravid et al., 1998).

Excellent protection against progression of renal damage in type 2 diabetics with varying degrees of proteinuria has been reported with ARBs—irbesartan in two trials (Lewis et al., 2001;, Parving et al, 2001), and losartan in the third (Brenner et al., 2001). Therefore, an ARB may be chosen as the initial drug, but there are no data showing that an ARB is superior to an ACEI. An ACEI may be used with an ARB, as the combination works better than moderate doses of either alone (Mogensen et al., 2000).

Because more than one drug will usually be needed, the second one chosen should likely be a diuretic, as volume expansion is usual with any degree of renal insufficiency. The third one could be a b-blocker, as atenolol was somewhat more effective than captopril in protecting the type 2 diabetics in the U.K. Prospective Diabetes Study (1998). On the other hand, a CCB may be needed to achieve BP control. If used alone, a CCB (particularly dihydropyridine), may (Tarnow et al., 2000a) or may not (Agodoa et al., 2001; Chan et al., 2000) slow the progression of renal disease as well as an ACEI but, in combination with an ACEI, CCBs are clearly safe and effective (Bakris et al., 2000b). Although an a-blocker, when used alone, increased the rate of heart failure in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT Officers and Coordinators, 2000), doxazosin was as effective as an ACEI in reducing proteinuria in type 2 diabetics (Rachmani et al., 1998).

In summary, the consensus report (Bakris et al., 2000b) states:

> Antihypertensive regimens should include an ACEI in order to provide maximum CV and renal benefits in this population. Data from several major recent prospective trials, including UKPDS [U.K. Prospective Diabetes Study] and HOT [Hypertension Optimal Treatment], demonstrate, however, that attainment of these lower goal blood pressures is virtually impossible to achieve with monotherapy. The majority of the time addition of multiple antihypertensive medications including a diuretic, CCB, or any similar combination is required to achieve these lower blood pressure goals.

Other Therapies

Although the evidence is not conclusive, a *low-protein diet* should be helpful (Mogensen, 2001). *Moderate sodium restriction* is clearly necessary (MacGregor, 2001), particularly as these patients tend to be very sensitive to the pressor effect of sodium (Imanishi et al., 2001). *Control of dyslipidemia* may also lower BP, reduce proteinuria (Tonolo et al., 2000), and slow the decline in GFR (Fried et al., 2001). As an aid to achieve control of hyperglycemia, a *thiazolidinedione* may also lower BP (Parulkar et al., 2001).

Gaede et al. (1999) have provided a striking demonstration of the ability of a multifaceted approach involving tight control of hypertension, hyperglycemia, and dyslipidemia, along with aspirin and an ACEI, to reduce the progression of nephropathy as well as retinopathy and autonomic neuropathy in patients with type 2 diabetes and microalbuminuria. Despite the costs and problems of such intensive therapy, the benefits are surely worth the expense and effort.

HYPERTENSION IN ACUTE RENAL DISEASE

Most acute, severe insults to the kidney result in decreased urine formation, retention of salt and water, and hypertension.

Acute Glomerulonephritis

The classic presentation of acute glomerulonephritis is a child with recent streptococcal pharyngitis or impetigo who suddenly passes dark urine and develops facial edema. The renal injury represents the trapping of antibody-antigen complexes within the glomerular capillaries. Although the syndrome has become less common, it still occurs, sometimes in adults past middle age. Typically, in the acute phase, patients are hypertensive, and there is a close temporal relation between oliguria, edema, and hypertension. On occasion, hypertension of a severe, even malignant, nature may be the over-riding feature.

The hypertension should be treated by salt and water restriction and, in mild cases, diuretics and other oral antihypertensives. In keeping with an apparent role of renin, ACEI therapy has been effective (Jardine, 1995). In the classic disease, the patient is free of edema and hypertension within days, of proteinuria within weeks, and of hematuria within months. Hypertension was found in only 3 of 88 children followed up for 10 to 17 years (Popovic-Rolovic et al., 1991).

More common than poststreptococcal glomerulonephritis are a variety of primary renal diseases (e.g., IgA nephropathy) and systemic diseases (e.g., systemic lupus erythematosus), which may present with acute renal crises marked by hypertension (Madaio and Harrington, 2001). The hypertension may be effectively treated with an ACEI (Steen and Medsger, 2000).

Acute Renal Failure

A rapid decline in renal function may appear from various causes: prerenal (e.g., volume depletion), intrinsic (e.g., glomerulonephritis), or postrenal (e.g., obstructive uropathy). NSAIDs are among the most common causes of acute renal failure, particularly in patients whose already reduced renal perfusion depends on prostaglandin-mediated vasodilation (Palmer and Henrich, 1995). Hypertension is rarely a problem, perhaps because peripheral vascular tone often is decreased. Now that dialysis is so readily available, the management of such patients is much less difficult, and virtually complete recovery, even after prolonged oliguria, is frequent.

Acute Urinary Tract Obstruction

Hypertension may develop after unilateral (Berka et al., 1994) or bilateral (Jones et al., 1987) obstruction to the ureters or the urethra (Robinson et al., 1992). Obstruction in rats is associated with activation of renin and suppression of kallikrein (El-Dahr et al., 1992). In such animals, ACEIs stop the development of intrarenal fibrosis from obstructive nephropathy (Ishidoya et al., 1996). In most patients, the hypertension is fairly mild, but significant hypertension and severe renal insufficiency may occur with hydronephrosis from prostatic obstruction (Sacks et al., 1989). Catheter drain-age of the residual urine may lead to rapid resolution of the hypertension and circulatory overload (Ghose and Harindra, 1989).

Other Causes of Acute Renal Disease

Other causes of acute renal disease include:

- Bilateral renal artery occlusion, either by emboli or thromboses.
- Removal of angiotensin II support of blood flow with ACEI therapy in the presence of bilateral renal artery disease (Textor and Wilcox, 2000)
- Trauma to the kidney (Watts and Hoffbrand, 1987).
- Cholesterol emboli, which may shower the kidney after radiologic or surgical procedures, producing rapidly worsening renal function and hypertension (Vidt, 1997).
- Extracorporeal shock wave lithotripsy for kidney stones, which may be followed by a rise in BP that lasts at least 6 months in 20% to 30% of patients (Hammond et al., 1993). The incidence of persistent hypertension seems quite small (Lingeman et al., 1995), but long-time follow-up is appropriate.

HYPERTENSION WITH RENAL PARENCHYMAL DISEASE BUT WITHOUT RENAL INSUFFICIENCY

The hypertension seen with all of the preceding renal diseases seems appropriate to the extensive renal damage, with resultant defects in salt and water excretion, renin secretion, or vasodepressor elaboration. Others of a more obvious vascular origin are covered in the next chapter. In some patients, however, hypertension is seen without enough overt renal damage or ischemia to explain the hypertension on any of these bases. This is particularly true in patients with unilateral renal parenchymal disease whose hypertension is relieved by removal of the afflicted kidney.

Renal Donors

In normal humans, the removal of a kidney usually does not result in hypertension, likely because of downward adjustments in glomerular hemodynamics to maintain normal fluid volume (Guidi et al., 2001). The issue has been recently explored more thoroughly because of the theoretic possibility—in keeping with the hyperperfusion theory (Fig. 9-2)—that removal of one kidney could lead to progressive glomerulosclerosis in the other.

No increase in the prevalence of hypertension was found in a metaanalysis of 48 studies with 2,988 patients who had had a unilateral nephrectomy and were carefully followed for a mean follow-up of 10.6 years (range, 2 to 50 years) (Kasiske et al., 1995). However, in a more recent study, 20 of 73 patients who had unilateral nephrectomy for various renal diseases developed proteinuria and CRD (Praga et al., 2000). Most of these 20 were obese.

As recently summarized (Gridelli and Remuzzi, 2000), “To date, the development of proteinuria in kidney donors has not been correlated with the development of hypertension or with the interval since nephrectomy; moreover, donors in whom proteinuria developed have not had progressive proteinuria or renal failure.”

Reflux Nephropathy and Pyelonephritis

Hypertensive children are frequently found to have pyelonephritic scarring, usually resulting from vesicoureteral reflux and urinary tract infection (Benador et al., 1997). Renal insufficiency and hypertension may not manifest for some years (Goonasekera et al., 1996). How-ever, in 255 patients with radiographically proved chronic pyelonephritis, if renal function was normal at presentation, reflected by a serum creatinine lower than 90 µmol/L, hypertension and proteinuria rarely appeared over a mean follow-up of 8 years (Goodship et al., 2000).

Drug-Induced Nephrotoxicity

Some patients thought to have chronic pyelonephritis actually have analgesic nephropathy from long-term, regular use of phenacetin, acetaminophen, or NSAIDs (Klag et al., 1996), a not uncommon cause of chronic renal failure in the United States (Griffin et al., 2000) but more common in Australia (Kincaid-Smith and Whit-worth, 1988). Because renal salt wasting is frequent with this form of interstitial nephritis, hypertension may be somewhat less common, but even malignant hypertension has been seen (Kincaid-Smith and Whitworth, 1988).

Other agents that induce hypertension are covered in Chapter 15.

Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the cause of 9% of cases of ESRD in the United States (U.S. Renal Data System, 2000). Hypertension is common, seen in 60% even without demonstrable renal insufficiency, and is usually accompanied by proteinuria (Ecder and Schrier, 2001). In more than 250 patients with ADPKD enrolled in clinical trials, neither the strict control of BP nor use of an ACEI provided the same benefits as seen in patients with proteinuric glomerulopathies (Torres, 2000). In a randomized, controlled trial in 24 ADPKD patients, treatment with enalapril reducedproteinuria better than did amlodipine but, after 5 years, both groups had equal control of BP and levels of renal function (Ecder et al., 2000). The investigators estimated that a delay of the onset of ESRD by 15 years was provided by effective control of hypertension.

Renal Tumors

As we shall see in the next chapter, renin-secreting tumors may cause severe hypertension. In addition to those rare tumors, hypertension may be seen with other renal tumors: nephroblastoma (Wilms' tumor), renal cell carcinoma, and hypernephroma. Most appear to cause hypertension by activation of the renin system.

Unilateral Renal Disease

In addition to these and other forms of renal disease, hypertension that is not secondary to obvious renal artery stenosis is not infrequently found in patients with small kidneys. After Goldblatt produced hypertension by unilateral renal ischemia, small kidneys were indiscriminately removed from hypertensive patients. Smith (1956) discouraged this practice by calling attention to a cure rate of only 26% in all reports published by 1956.

In most patients cured by unilateral nephrectomy, renovascular disease—not primary parenchymal disease—is probably the cause for both the atrophic kidney and the hypertension, presumably by means of the renin mechanism. Renin levels are increased in the venous blood coming from many of those kidneys, the removal of which results in relief of hypertension (Gordon et al., 1986). On the other hand, there are reports of cure of hypertension by removal of kidneys thought to be atrophic because of parenchymal disease, usually pyelonephritis, and not because of vascular impairment, as reflected by the presence of normal renin levels (Lamberton et al., 1981).

In view of these questions concerning both the frequency and mechanism of unilateral parenchymal disease as a cause of hypertension, caution is advised before nephrectomy is performed in such patients. The cure rate with parenchymal atrophy is probably much less than that with vascular disease. Nephrectomy should be reserved for patients with the following conditions:

- Severe hypertension.
- Marked loss of renal function in the afflicted kidney that should be recognizable by renal scintigraphy. (In practice, a renal size of <8.5 cm usually denotes an inability to salvage the kidney by revascularization.)
- Normal renal function in the other kidney.

We next turn to the disease in which surgical relief and renin are more closely connected: renovascular hypertension.

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*The management of hypertension in diabetics without nephropathy is covered in Chapter 7.

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10
Renovascular Hypertension

Renovascular hypertension (RVHT), usually caused by renal artery stenosis, is one of the more common forms of identifiable hypertension; reports of its frequency vary from less than 1% in unselected populations to as many as 50% of patients selected for various special features. It is important to consider because, if identified, it is curable; if left untreated, it may destroy the kidneys. The presence of bilateral renal artery stenosis should be considered in all patients with unexplained chronic or progressive renal insufficiency, because ischemic nephropathy may be involved in one-fourth of such patients (Safian and Textor, 2001).

RENOVASCULAR DISEASE VERSUS RENOVASCULAR HYPERTENSION

Renovascular hypertension refers to hypertension caused by renal ischemia. It is important to realize that renovascular *disease* may or may not cause sufficient hypoperfusion to set off the processes that lead to hypertension. The problem is simply that renovascular disease is much more common than is RVHT. For example, arteriography revealed some degree of renal artery stenosis in 32% of 303 normotensive patients and in 67% of 193 hypertensives with an increasing prevalence with advancing age (Eyler et al., 1962) (Table 10-1). Note that in Table 10-1 almost half of *normotensive* patients older than 60 had atherosclerotic lesions in their renal vessels.

	Normotensive (n = 304)		Hypertensive (n = 193)	
Age (yr)	Normal	Lesion	Normal	Lesion
31–40	7	3	6	10
41–50	26	8	14	22
51–60	99	35	28	50
60+	69	56	15	48

Data from Eyler WR, Clark MD, Garman JE, et al. Angiography of the renal areas including a comparative study of renal arterial stenoses in patients with and without hypertension. *Radiology* 1962;78:879–892.

TABLE 10-1. *Prevalence of renal arterial lesions in normotensive and hypertensive patients*

Before procedures were available to prove the functional significance of stenotic lesions, surgery was frequently performed on hypertensive patients with a unilateral small kidney who did not have reversible RVHT. Homer Smith (1956) recognized this as early as 1948 as a misguided application of Goldblatt's experimental model of hypertension induced by clamping the renal artery. Smith reported that only 25% of patients were relieved of their hypertension by nephrectomy and warned that only about 2% of all hypertensives probably could be helped by surgery.

PREVALENCE OF RENOVASCULAR HYPERTENSIONM

Smith's (1956) estimate of the true prevalence of RVHT may be right. The prevalence varies with the nature of the hypertensive population:

- In nonselected patient populations, the prevalence is less than 1% (see Chapter 1, Table 1-7).
- Among patients referred for diagnostic studies, as many as 10% have RVHT (Bijlstra et al., 1996). A similar prevalence was found in patients with hypertension resistant to two drugs (van Jaarsveld et al., 2001).
- In patients with suggestive clinical features, the prevalence is higher; among 490 patients with severe, resistant, or rapidly progressive hypertension, RVHT was found in 50 of 338 patients (15%) older than 40 (Horvath et al., 1982). However, in the study by Radermacher et al. (2001), only 2.3% of 5,950 hypertensives with suggestive clinical features had at least a 50% stenosis of one or both renal arteries by color Doppler ultrasonography.
- Among patients with accelerated-malignant hypertension, the prevalence is even higher (Webster et al., 1993): Of 123 adults with diastolic blood pressure (BP) greater than 125 mm Hg and grade III or IV retinopathy, 4% of blacks and 32% of whites had RVHT (Davis et al., 1979). RVHT is responsible for one-third of end-stage renal disease cases in patients older than 65 years in Europe (Gómez-Campderá et al., 1998).
- Renal artery stenosis also is seen more frequently in hypertensive patients with atherosclerotic disease in peripheral (Leertouwer et al., 2001), carotid, or coronary arteries (Conlon et al., 2000); in elderly patients with heart failure (Missouris et al., 2000); and in patients with severe hypertension and rapidly progressing renal insufficiency, particularly if it develops after institution of angiotensin-converting enzyme inhibitor (ACEI) therapy (Brunner, 1992). On the other hand, RVHT is less common in blacks; in one series, it was found in 12% of blacks versus 28% of whites (Hansen et al., 1998). Diabetics, even though they have a higher prevalence of renal artery stenosis, have less RVHT (Valabhji et al., 2000).
- RVHT has been recognized in neonates (Tapper et al., 1987), children (Liang et al., 1996), and pregnant women (Keely, 1998).

MECHANISMS OF HYPERTENSION

Animal Models

Although Franz Volhard and his students supported a pressor role for renal ischemia even earlier (Wolf, 2000), the pathophysiology of RVHT was first identified by

Goldblatt et al. (1934) who, looking not for RVHT but for a renal cause for essential hypertension, put clamps on both renal arteries of dogs. The clamps were inserted on separate occasions so that they could observe the effect of unilateral obstruction (Fig. 10-1). However, with the modest degree of constriction that they used, unilateral clamping caused only transient hypertension. For permanent hypertension, both renal arteries had to be clamped, or one clamped and the contralateral kidney removed (Goldblatt, 1975). Sheep and rats have been found to be particularly susceptible to two-kidney, one-clip hypertension, so they are better models for humans than are dogs and rabbits (Schoenberg et al., 2000).

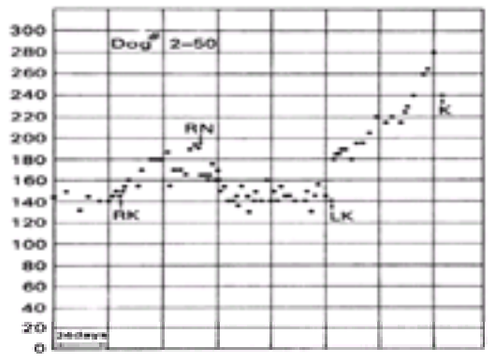


FIG. 10-1. Results from one of Goldblatt's original experiments. The graph shows the mean blood pressure of a dog whose right kidney was first moderately constricted (RK), with subsequent hypertension that was relieved after right nephrectomy (RN). After severe constriction of the left renal artery (LK), more severe hypertension occurred, and the animal was sacrificed (K). (Reprinted from Hoobler SW. History of experimental renovascular hypertension. In: Stanley JC, Ernst CB, Fry WJ, eds. *Renovascular hypertension*. Philadelphia: Saunders, 1984:12–19, with permission.)

After significant renal ischemia and the initial marked rise in renin secretion, renin levels fall but remain inappropriately high and are largely responsible for the hemodynamic changes (Welch, 2000). Figure 10-2 shows a stepwise scheme for the hemodynamic and hormonal changes that underlie RVHT.

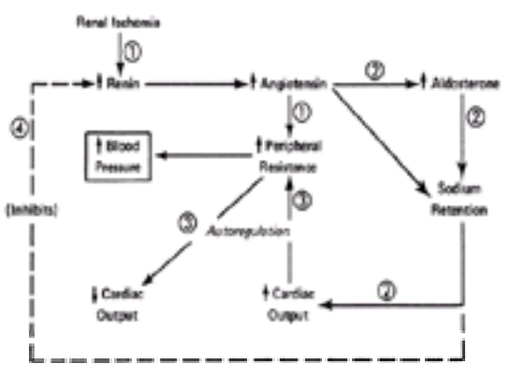


FIG. 10-2. Hypertension with renovascular disease. Stepwise hemodynamic changes in the development of renovascular hypertension.

Other factors may be involved that interrelate to these primary mechanisms, including the following:

- Activation of the sympathetic nervous system (Johansson and Friberg, 2000)
- Vasopressin (Ichikawa et al., 1983)
- Progressive structural thickening of small arteries both inside (Anderson et al., 2000) and outside (Rizzoni et al., 2000) the kidney
- Increased lipoxygenases (Romero et al., 1997) and thromboxane (Martinez-Maldonado, 1991), likely involved in the significant fall in BP noted in patients with RVHT who were given aspirin (Imanishi et al., 1989)
- Increased levels of atrial natriuretic factor, kallikrein (Martinez-Maldonado, 1991), vasodilative prostaglandins (Milot et al., 1996), and nitric oxide (Nakamoto et al., 1995), which may counter the effects of the activated reninangiotensin system.

Studies in Humans

As in the animal models, RVHT in humans is caused by increased renin release from the ischemic kidney (Welch, 2000). Simon (2000) suggests that the stenosis must obstruct at least 80% of the arterial lumen to set off the process. An immediate release of renin has been measured in patients whose renal perfusion pressure was acutely reduced by a balloon-tipped catheter (Fiorentini et al., 1981). The high level of angiotensin II increases renal vascular resistance, causing a shift in the pressure-natriuresis curve; thus, volume is maintained despite markedly elevated BP (Granger and Schnackenberg, 2000). Chronically, the ischemic kidney continues to secrete excess renin and BP falls when angiotensin antagonists are given. When the stenosis is relieved, hypertension recedes by a fall in peripheral resistance and fluid volume (Valvo et al., 1987).

As in animal models, humans may enter into a third phase, wherein removal of the stenosis or the entire affected kidney will not relieve the hyper-tension because of widespread arteriolar damage and glomerulosclerosis in the contralateral kidney by prolonged exposure to high BP and high levels of angiotensin II (Kimura et al., 1991). This phenomenon is clinically relevant: The sooner an arterial lesion that is causing RVHT is removed, the greater the chance of relieving the hypertension. Among 110 patients, corrective surgery for unilateral RVHT was successful in 78% of those with hypertension of less than 5 years' duration but in only 25% of those with hypertension of longer duration (Hughes et al., 1981).

CLASSIFICATION AND COURSE

The most common cause of RVHT is atherosclerotic stenosis of the main renal artery; most of the remaining cases are fibroplastic, but a number of both intrinsic and extrinsic lesions can induce RVHT (Table 10-2). The general features of the most common types of renal artery stenosis are listed in Table 10-3.

TABLE 10-2. *Types of lesions associated with renovascular hypertension*

Renal artery disease history	Incidence (%)	Age (yr)	Location of lesion in renal artery	Natural history
Atherosclerosis	80–90	>50	Proximal 2 cm; branch disease rare	Progression in 50% often to total occlusion
Fibromuscular dysplasia				
Intimal	1–2	Children, young adults	Middle main renal artery and branches	Progression in most cases dissection or thrombosis (or both) common
Medial	10–20	25–50	Distal main renal artery and branches	Progression in 33%; dissection or thrombosis rare
Periarterial	1–2	15–30	Middle to distal main renal artery or branches	Progression in most cases dissection or thrombosis common

TABLE 10-3. *Features of the two major forms of renal artery stenosis*

Atherosclerotic Lesions

As compared to patients with primary hypertension, patients with atherosclerotic RVHT are older and have higher systolic pressure, more extensive renal damage, and vascular disease elsewhere (Connolly et al., 1994); more extensive left ventricular hypertrophy; ischemic heart disease; and renal insufficiency (Rizzoni et al., 1998). Black patients with RVHT tend to have even more severe hypertension and extrarenal vascular disease than do white patients with RVHT (Novick et al., 1994).

The natural history of atherosclerotic renal artery stenosis has been ascertained by repeated renal artery duplex scans in a total of 295 kidneys in 170 patients over a mean of 33 months (Caps et al., 1998a). As seen in Figure 10-3, progression was common in those with initially high-grade (³60%) stenoses accompanied by a 21% incidence of renal atrophy, defined as a 1-cm or greater decrease in renal length (Caps et al., 1998b). Progression was associated with a systolic BP of 160 mm Hg, diabetes mellitus, and high-grade stenoses in either the ipsilateral or the contralateral kidney.

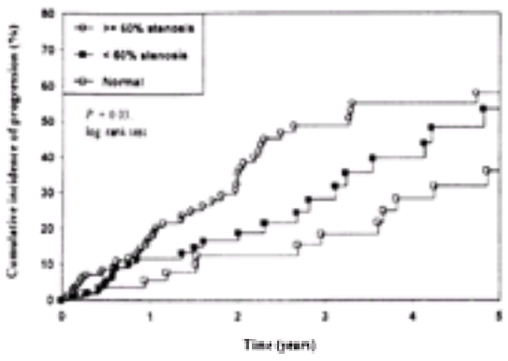


FIG. 10-3. Cumulative incidence of renal disease progression stratified according to baseline degree of renal artery narrowing. Standard errors were <10% for all plots through 5 years. (Reprinted from Caps MT, Perissinotto C, Zierler E, et al. Prospective study of atherosclerotic disease progression in the renal artery. *Circulation* 1998a;98:2866–2872, with permission.)

A less progressive loss of renal function has been observed in two studies of patients with at least a 50% renal artery stenosis, recognized incidentally during angiography for coronary (Conlon et al., 2000) or peripheral (Leertouwer et al., 2001) vascular disease. Even though the degree of renal artery stenosis was at least 70% in a significant portion of these patients, end-stage renal failure developed in only 1 of the 188 with coronary disease over 4 years and in none of the 126 with peripheral vascular disease over 10 years. Therefore, as Leertouwer et al. (2001) wrote, “The current trend toward aggressive interventional treatment of incidentally found renal artery stenosis may need careful reappraisal.” At the least, a clear distinction should be made between the likelihood of progression of renal artery disease identified in patients with clinically suggestive features of RVHT and evidence of renal ischemia, on the one hand, and patients with no clinical or functional evidence of RVHT, on the other.

Segmental lesions, usually stenosis of only a small branch supplying a portion of one kidney, were found in 11% of the patients in the large Cooperative Study of Renovascular Hypertension (Bookstein, 1968).

Fibromuscular Dysplasia

As seen in Figure 10-4, three types of fibromuscular stenoses were defined by investigators at the Mayo Clinic (Lüscher et al., 1987). Of these, medial fibroplasia is the most common, whereas focal fibroplastic lesions are more common in children (Stanley et al., 1978).

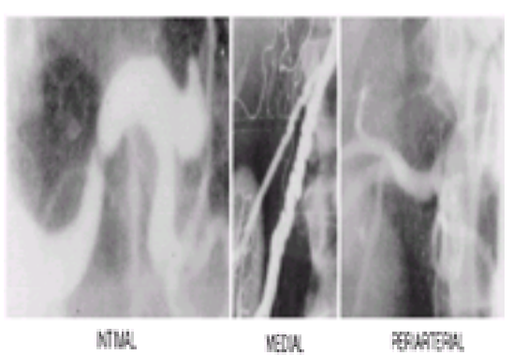


FIG. 10-4. Representative radiographs of the three major types of fibromuscular dysplasia. (Reprinted from Lüscher TF, Lie JT, Stanson AW, et al. Arterial fibromuscular dysplasia. *Mayo Clin Proc* 1987;62:931–952, with permission.)

Medial fibromuscular dysplasia is usually noted in young women but has been found in an 80-year-old (Prieto et al., 1996). The process often involves multiple arteries arising from the aorta, including the carotid and celiac vessels (Lüscher et al., 1987). Half of the patients with bilateral renal artery medial fibroplasia have extrarenal disease as well, which is rarely symptomatic. As compared with atherosclerotic disease, a progressive course may be less frequently seen with medial fibroplasia. The following features were found more commonly in 33 patients with medial fibromuscular dysplasia than in 61 subjects with normal renal arteries: cigarette smoking, HLA-DRw6 antigen, and a family history of cardiovascular disease (Sang et al., 1989). On the other hand, there was no association with oral contraceptive use, abnormal endogenous sex hormone levels, or increased renal mobility. The association with smoking has been repeatedly noted (Bofinger et al., 1999).

Patients with the less common but more sharply localized fibroplastic lesions—intimal and periarterial—usually show rapid progression, so severe stenosis and

hypertension are frequently observed (Pickering, 1989). With intravascular ultrasonography, focal narrowing of an otherwise normal renal artery (i.e., coarctation) was found in 9 of 18 patients with presumably atherosclerotic renal vascular disease (Leertouwer et al., 1999a).

Other Causes

Of the myriad causes of renovascular hypertension listed in Table 10-2, a few deserve additional comment.

Aneurysm

Aneurysms are common with medial fibroplasia. Saccular aneurysms, usually at the bifurcation of the renal artery, may induce hypertension by various mechanisms. They rarely rupture and need not be ablated if less than 1.5 cm in diameter (Lebel and Laroche, 1998).

Emboli

Most commonly seen as a complication of angiography or vascular surgery, renal cholesterol emboli can induce subacute renal failure or RVHT (Dupont et al., 2000). Cutaneous and other visceral lesions are usually seen, but the diagnosis may be documented only by renal biopsy.

Arteritis

Progressive aortic arteritis (Takayasu's arteritis) is seen infrequently in North America and Europe but is a common cause of RVHT in China, India, Japan, Mexico, and Brazil (Machado et al., 2000; Numano et al., 2000). Although glucocorticoids have been used, greater success has been reported with angioplasty (Sharma et al., 1996).

RVHT is common in various vasculitic syndromes with renal involvement, including Wegener's granulomatosis (Woodrow et al., 1990), systemic lupus erythematosus (Ward and Studenski, 1992), and the antiphospholipid syndrome (Riccialdelli et al., 2001). These patients may enter into an acute, severe hypertensive phase, usually associated with markedly elevated plasma renin levels, likely reflecting intrarenal stenoses from multiple arteriolar lesions. The hypertension can sometimes be rather remarkably reversed by ACEI therapy (Coruzzi and Novarini, 1992).

Dissection

RVHT was found in nearly 20% of patients with aortic dissection (Rackson et al., 1990).

Nephroptosis

Increased mobility of the kidney of 7.5 cm or more as the patient moves from the supine to the upright position (nephroptosis) has been associated with this form of RVHT (de Zeeuw et al., 1977), although such ptosis was not observed in the 33 patients with medial fibroplasia seen by Sang et al. (1989).

CLINICAL FEATURES

General

Clinical features suggestive of renovascular disease as the cause of hypertension are presented in Table 10-4 (McLaughlin et al., 2000). Some of these features were identified in a cooperative study involving 2,442 hypertensive patients, 880 with renovascular disease (Maxwell et al., 1972). Of the 880, 502 had surgery; of these, 60% had atherosclerotic lesions and 35% had fibromuscular disease. Table 10-5 compares the clinical characteristics of 131 patients with surgically cured renovascular disease and a carefully matched group with essential hypertension (Simon et al., 1972).

History
Onset of hypertension before age 30 or after age 50
Abrupt onset of hypertension
Severe or resistant hypertension
Symptoms of atherosclerotic disease elsewhere
Negative family history of hypertension
Smoker
Worsening renal function with angiotension-converting enzyme inhibition
Recurrent flash pulmonary edema
Physical examination
Abdominal bruits
Other bruits
Advanced fundal changes
Laboratory findings
Secondary aldosteronism
Higher plasma renin
Low serum potassium
Low serum sodium
Proteinuria, usually moderate
Elevated serum creatinine
>1.5-cm difference in kidney size on sonography

Adapted from McLaughlin K, Jardine AG, Moss JG. Renal artery stenosis. BMJ 2000;320:1124–1127.

TABLE 10-4. *Clinical clues for renovascular hypertension*

Characteristics	Essential hypertension (%)	Renovascular hypertension (%)
Duration of hypertension <1 yr	12	24
Age at onset after 50	9	15
Family history of hypertension	71	46
Grade 3 or 4 fundoscopic changes	7	15
Abdominal bruit	9	46
Blood urea nitrogen >20 mg/dL	8	15
Serum potassium <3.4 mEq/L	8	16
Urinary casts	9	20
Proteinuria	32	46

Reprinted from Simon N, Franklin SS, Bleifer KH, Maxwell MH. Clinical characteristics of renovascular hypertension. JAMA 1972;220:1209, with permission.

TABLE 10-5. *Clinical characteristics of 131 patients with proved renovascular hypertension as compared with a matched group of patients with essential hypertension*

Of the clinical features more common in patients with RVHT, only an abdominal bruit was of clear discriminatory value, heard in 46% of those with RVHT but in only 9% of those with essential hypertension. The bruit was heard over the flank in 12% of those with RVHT and in only 1% of those with essential hypertension. As nicely reviewed by Turnbull (1995) , most systolic bruits are innocent, but systolic-diastolic bruits in hypertensives are suggestive of RVHT.

Hyperaldosteronism

Patients with RVHT occasionally have profound secondary aldosteronism with hypokalemia due to urinary potassium wasting and low serum sodium (Agarwal et al., 1999)—all reversed with relief of RVHT.

Nephrotic Syndrome

Proteinuria is common, and a few patients with RVHT have nephrotic-range proteinuria, usually with more severe renal damage and, often, renal artery thrombosis (Halimi et al., 2000).

Polycythemia

Polycythemia has been seen occasionally in patients with RVHT (Hudgson et al., 1967); more common are elevated peripheral and renal venous erythropoietin levels without polycythemia (Grützmacher et al., 1989).

Dyslipidemia

Not surprisingly, those with atherosclerotic RVHT may have dyslipidemia, in particular low apolipoprotein A_1 levels (Scoble et al., 1999). Correction of dyslipidemia may reverse RVHT (Basta et al., 1976).

Ischemic Nephropathy

Ischemic nephropathy is defined as renal dysfunction secondary to ischemia, usually from bilateral renal artery stenoses. Bilateral stenosis develops within 2 years in up to 18% of patients with unilateral atherosclerotic renal artery stenosis (Safian and Textor, 2001) and was present in 28% of the patients in the cooperative study (Bookstein et al., 1977). Such bilateral disease is estimated to be responsible for 38% of end-stage renal disease in the elderly (Gómez-Campderá et al., 1998). Because unilateral RVHT is not associated with an elevated serum creatinine, an increase to more than 2 mg/dL in a patient with known unilateral RVHT suggests the development of bilateral stenoses (Safian and Textor, 2001).

Such patients with ischemic nephropathy may be difficult to distinguish from the larger number with essential hypertension or primary renal parenchymal disease who progress into renal failure (Textor and Wilcox, 2000). The recognition is important, because surgical repair or angioplasty may relieve both the hypertension and the renal failure (Nickeleit et al., 1999; Ying et al., 1984).

The possibility of bilateral renovascular disease should be considered in the following groups:

- Young women with severe hypertension, in whom fibroplastic disease is common.
- Older patients with extensive atherosclerotic disease who suddenly have a worsening of renal function (Conlon et al., 2000).
- Azotemic hypertensives who develop multiple episodes of acute pulmonary edema (Missouris et al., 2000).
- Any hypertensive who develops rapidly progressive renal failure without evidence of obstructive uropathy (Baboolal et al., 1998).
- Patients in whom renal function quickly deteriorates after treatment with an ACEI or other antihypertensive therapy. A controlled exposure to an ACEI has been proposed to be an accurate and safe test for detecting bilateral RVHT (van de Ven et al., 1998).

Such patients, if they are candidates for intervention, should have an appropriate workup to determine the presence of occlusive disease, but no controlled trials in such patients have been performed to determine the best strategy.

Variants

Hypertension from Contralateral Ischemia

Hypertension may start with renal stenosis on one side but may persist because of damage to the nonstenotic kidney by the hypertension and high renin (McAllister et al., 1972; Thal et al., 1963).

Hypertension after Renal Transplantation

As described in Chapter 9, patients who develop severe hypertension after successful renal transplantation should be evaluated for stenosis of the renal artery. These patients have the same propensity for marked loss of renal function if treated with an ACEI as do patients with bilateral RVHT.

Hypertension and the Hypoplastic Kidney

As described in Chapter 9, most patients with a small kidney but without a stenotic lesion who respond to nephrectomy have increased plasma renin activity (PRA) from the venous blood draining the diseased kidney, suggesting a renovascular etiology (Mizuiri et al., 1992). The continued secretion of renin is an indication of viability, despite the absence of excretory function and the presence of severe tubular atrophy on biopsy. Revascularization, preferably by angioplasty, should always be considered, because remarkable return of renal function may follow, even when the kidney appears to be nonfunctioning.

Even with a unilateral small kidney, hypertension may arise from renovascular disease in the contralateral kidney. Such was the situation in a young woman with fibroplastic renovascular disease and renal failure whose hypertension was relieved by relief of the stenosis without surgery on the small kidney (Nickeleit et al., 1999).

DIAGNOSTIC TESTS

Mann and Pickering (1992) have formulated a useful guide to the diagnostic workup for RVHT based on “a selective approach in which only patients with suggestive clinical clues are tested.” They provide the index of clinical suspicion (Table 10-6) and then a suggested workup for patients in the low, moderate, and high categories. Near the end of this chapter, an overall scheme based on this index for evaluation of and therapy for RVHT is presented. Van Jaarsveld and Krijnen (2000) have presented a more formal “clinical prediction rule” for quantifying the probability of renal artery stenosis to help select patients for arteriography. One caveat is obvious: If patients are not candidates for surgery or angioplasty, they should not be subjected to the various procedures needed to make the diagnosis.


Low index of suspicion (should not be tested)
Borderline, mild to moderate hypertension, in the absence of clinical clues
Moderate index of suspicion (noninvasive tests recommended)
Severe hypertension (DBP >120 mm Hg)
Hypertension refractory to standard therapy excluding ACEI or ARB
Abrupt onset of sustained, moderate to severe hypertension at age <30 yr or >50 yr
Hypertension with a suggestive abdominal or flank bruit
Moderate hypertension (DBP >105 mm Hg) in a smoker, a patient with evidence of occlusive vascular disease (cerebrovascular, coronary, peripheral vascular), or a patient with unexplained but stable elevation of serum creatinine
Normalization of blood pressure by an ACEI or ARB in a patient with moderate to severe hypertension (particularly a smoker or a patient with recent onset of hypertension)
High index of suspicion (may consider proceeding directly to arteriography)
Severe hypertension (DBP >120 mm Hg) with other progressive renal insufficiency or retinopathy to aggressive treatment, particularly in a patient who has been a smoker or has other evidence of occlusive arterial disease
Accelerated or malignant hypertension (grade III or IV retinopathy)
Hypertension with recent elevation of serum creatinine, either unexplained or reversibly induced by an ACEI or ARB
Moderate to severe hypertension with incidentally detected asymmetry of renal size

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DBP, diastolic blood pressure.

Modified from Mann SJ, Pickering TG. Detection of renovascular hypertension. State of the art. 1992. Ann Intern Med 1992; 117:845–853.

TABLE 10-6. *Testing for renovascular hypertension: clinical index of suspicion as a guide to selecting patients for workup*

The majority of patients with no suggestive features would get no further workup. Those with features that indicate a moderate (from 5% to 15%) likelihood of RVHT

should be screened with a captopril-augmented renal scan with simultaneous measurement of peripheral blood PRA. Although color duplex ultrasonography and magnetic resonance angiography (MRA) are alternatives favored by some (De Cobelli et al., 2000; Pedersen, 2000; Vasbinder et al., 2001), they are less attractive because of the need for expert training of the personnel performing the former and the high cost of the latter. The relatively few patients with highly suggestive features should have an arteriogram, likely without the other screening studies.

The various tests now used to screen and diagnose renovascular disease will be described; they are grouped into those that assess renal perfusion, those that measure renin levels, and those that visualize the renal arteries.

Tests of Renal Perfusion

Intravenous Pyelography

After Maxwell et al. (1964) showed the advantages of rapid-sequence intravenous pyelography, this procedure became accepted as the best initial screening test for RVHT. Although rarely used for that purpose now, it has been argued that the procedure is the best initial test to screen for both renal parenchymal and vascular causes of hypertension (Cameron et al., 1992).

Renal Scan

Renography may be done with radiolabeled agents that are excreted either by glomerular filtration—technetium-99 diethylenetriamine pentaacetic acid (^{99}Tc-DTPA)—or partially by filtration but mainly by tubular secretion to measure renal blood flow— ^{131}I-hippurate, or ^{99}Tc-mercaptoacetyltriglycine (^{99}Tc-MAG$_3$).

Both the scintigraphic images and the time-activity curves should be measured. Nally et al. (1991) propose a grading system for the interpretation of renograms and suggest that the probability of functionally significant renal artery stenosis after captopril challenge be defined as “low, indeterminate or high.” When used alone, isotopic renograms provided approximately 75% sensitivity and specificity for the diagnosis of RVHT (Pickering, 1991).

Captopril-Enhanced Renal Scan

Soon after the observation that renal function in an ischemic kidney could abruptly be reduced further after a single dose of the ACEI captopril (Hricik et al., 1983), the effect of captopril on renal uptake of ^{99}Tc-DTPA was reported (Wenting et al., 1984). Either a reduction of the uptake of ^{99}Tc-DTPA or a slowing of the excretion of ^{131}I-hippurate or ^{99}Tc-MAG$_3$ can be used to identify the effect of the ACEI in removing the protective actions of the high levels of angiotensin II on the autoregulation of glomerular filtration and on the maintenance of renal blood flow, respectively (Fig. 10-5).

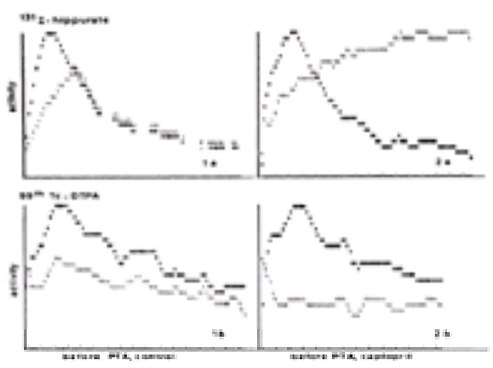


FIG. 10-5. Renography in a 42-year-old man with hypertension and stenosis of the left renal artery. L, left kidney; R, right kidney. After percutaneous transluminal angioplasty (PTA), his hypertension was cured. The upper half of the figure shows ^{131}I-hippurate (a) and the lower half shows ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) (b) time-activity curves in two different circumstances: (1) before PTA without any medication (control) and (2) before PTA but with 25 mg captopril taken orally 1 hour before the investigation. Captopril slowed down the excretion of ^{131}I-hippurate and reduced the uptake of ^{99m}Tc-DTPA in only the left kidney. (Reprinted from Geyskes GG, Oei HY, Puylaert BAJ, Mees EJD. Renovascular hypertension identified by captopril-induced changes in the renogram. *Hypertension* 1987;9:451–458, with permission.)

As reviewed by Taylor (2000), ACEI renography is highly accurate in patients with a moderate likelihood of renovascular hypertension and normal renal function, wherein sensitivity and specificity are approximately 90%. By combining data from ten studies that evaluated the effects of revascularization in 291 patients, the mean positive predictive value of ACEI renography was 92%. As expected, the test is less sensitive in patients with renal insufficiency; as many as half will have an indeterminate test. In a subsequent metaanalysis of 14 studies, ACEI renography provided diagnostic accuracy similar to ultrasonography (Vasbinder et al., 2001).

The test may give false-negative results in some patients with small ischemic kidneys and evidence of unilateral disease when bilateral disease is present (Scoble et al., 1991). However, it can be used in patients with a solitary kidney (Fanti et al., 1993). The test can be done in patients taking various antihypertensive drugs, although sensitivity is reduced in patients who are on ACEI therapy (Pedersen, 2000).

To reduce the cost and time of the workup, the postcaptopril renal scan should be done first. If the result is negative (as it will be most of the time), there is no need for a precaptopril renogram. If the test is positive, the procedure should be repeated without captopril to ensure that the differences are related to reversible vascular disease and not parenchymal damage.

Tests Assessing Renin Release

Peripheral Blood Plasma Renin Activity

Because hypersecretion of renin from the hypoperfused kidney is the primary event in the pathogenesis of RVHT, it came as no surprise that increased peripheral PRA levels were found in patients with the disease. However, subsequent experience with PRA assays in peripheral blood showed that many patients with RVHT did not have elevated levels (Rudnick and Max-well, 1984), in keeping with the experimental evidence that secretion of renin from the clipped kidney falls to “normal” soon after RVHT is induced, whereas renin release from the contralateral kidney is suppressed.

Captopril-Enhanced Peripheral Plasma Renin Activity

Various maneuvers have been used to augment PRA release in the hope that patients with curable disease would show a hyperresponsiveness, thereby improving the discriminatory value of peripheral levels (Wilcox, 2000). Of these, the response of PRA to captopril has been most widely used (Muller et al., 1986). Subsequently, a high rate of false-positive captopril renin tests was noted in patients with baseline high PRA levels (Gerber et al., 1994). The criteria for a positive test have been lowered; Wilcox (2000) uses a postcaptopril PRA level in excess of 5.4 ng per mL per hour. Whatever the criteria, the test has been found to have limited value as a screening study (Vasbinder et al., 2001).

Comparison of Renal Vein Renins

The comparison of renin levels in blood from each renal vein, obtained by percutaneous catheterization, has been used to establish both the diagnosis and surgical curability of RVHT since the initial report by Helmer and Judson (1960). In most series, a ratio greater than 1.5:1.0 between the two renal vein PRA levels was considered abnormal, or lateralizing. An abnormal ratio was 92% predictive of curability; however, 65% of those whose renal vein PRA level ratio did not lateralize

also were improved by surgery (Rudnick and Maxwell, 1984).

This procedure cannot be used as a screening test, but it may be useful in confirming the functional significance of a lesion demonstrated by arteriography, particularly if bilateral disease is noted. However, the captopril renogram will serve that purpose in addition to providing a more reliable screening test. Therefore, renal vein renin measurements are being used less and less.

Tests Imaging the Renal Arteries

Color Doppler Ultrasonography

Over the last 10 years, ultrasonography has progressed from M-mode scanning to Doppler and now to color Doppler (Pedersen, 2000) and, in some places, intravascular ultrasonography (Leertouwer et al., 1999b). Multiple indices of flow characteristics have been used (Fig. 10-6). The diagnostic value of color Doppler sonography has been improved by the use of an intrarenal measurement, determination of resistive index and pulsatility index in both kidneys. With such an approach, technical failures have been eliminated, the time for the test reduced to 15 to 20 minutes, and the sensitivity and specificity for detection of a significant stenosis as compared to angiography increased to 98% (Radermacher et al., 2000).

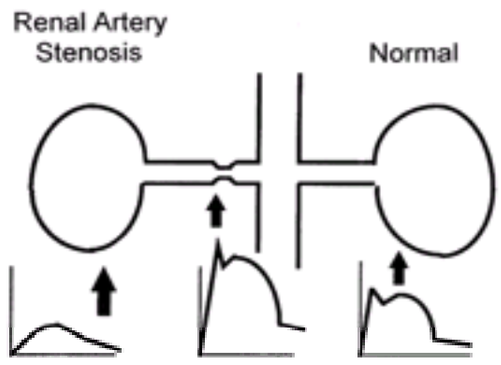


FIG. 10-6. Schematic diagram of renal artery Doppler tracings. The tracing on the right is of a normal renal artery; in the middle, of high velocity measured at the stenosis in the renal artery; on the left, of a dampened waveform measured downstream from the stenosis. (Reprinted from Mitty HA, Shapiro RS, Parsons RB, Silberzweig JE. Renovascular hypertension. *Radiol Clin North Am* 1996;34:1017–1036, with permission.)

As a result of these refinements, color Doppler ultrasonography is increasingly being advocated as the first choice for screening for RVHT (Johansson et al., 2000). Radermacher et al. (2001) have found the resistance index, defined as [1 – (end-diastolic velocity ÷ maximal systolic velocity)] ¥ 100, to be the best predictor of improvement after therapy. Those with a resistance index higher than 80 did poorly; their high vascular resistance presumably reflects irreversible structural damage to the renal vasculature distal to the stenosis, induced by prolonged hypertension.

Renal Arteriography

Rationale

The various tests described in the preceding sections are often recommended before renal arteriography. However, more and more experience seems to confirm the wisdom of a modified Willie Sutton's law: “If you are searching for a lesion, look at the vessel.” This seems particularly true for those with highly suggestive clinical features in whom negative screening tests would not be enough to exclude the diagnosis, thus necessitating arteriography regardless of those tests' outcome.

The reasons for choosing renal arteriography as the initial study in patients with features highly suggestive of RVHT include the following:

- Arteriography provides an immediate answer to the question, Is there renovascular disease that is potentially curable? None of the other studies can rule out reversible renovascular disease with certainty. Neither MRA nor spiral computed tomographic angiography can visualize intrarenal branch lesions as well (Pedersen, 2000).
- If a significant stenosis is found, percutaneous angioplasty may be immediately performed (Bonelli et al., 1995).
- With digital subtraction angiography, small catheters and small quantities of dye are needed so that discomfort and danger for the patient are minimal (Hillman, 1989). The danger of contrast material–induced renal damage is small and can be further minimized by adequate hydration and avoidance of non-steroidal antiinflammatory agents (Barrett et al., 1992). A few investigators use carbon dioxide as the contrast agent, to reduce further the potential for renal damage (Caridi et al., 1999).
- Knowledge of the renal vascular architecture is helpful before collection of renal vein renin samples and is essential before either angioplasty or surgery.

Prognostic Accuracy

Renal arteriography is almost always successful in diagnosing renal artery stenosis, but it may not distinguish between “critical” (>70%) and “non-critical” (<60%) stenoses (van Jaarsveld et al., 1999). It is of relatively little value, moreover, in determining curability of RVHT. In the cooperative study, the degree of stenosis, the presence of poststenotic dilatation, and the presence of collateral circulation were of no significant discriminatory value in predicting success or failure of surgery (Bookstein et al., 1972). In patients with apparently totally occluded main renal arteries, the finding of a markedly delayed and reduced nephrogram is a useful indicator of irreversible renal damage that likely will not respond to revascularization (Feltrin et al., 1986).

Spiral Computed Tomography and Magnetic Resonance Angiography

Both spiral computed tomography and MRA are being increasingly used to visualize the renal arteries, to reduce the dangers of contrast media nephropathy and cholesterol embolization (Pedersen, 2000). The most important advantages of spiral computed tomographic angiography are the injection of contrast medium intravenously rather than directly into the renal arteries, the ability to visualize both the arterial lumen and wall in three dimensions, and the ability to visualize accessory and distal vessels (Fig. 10-7). Both the quality and ease of the procedure are improved with multidetector row scanners (Rubin, 2001).

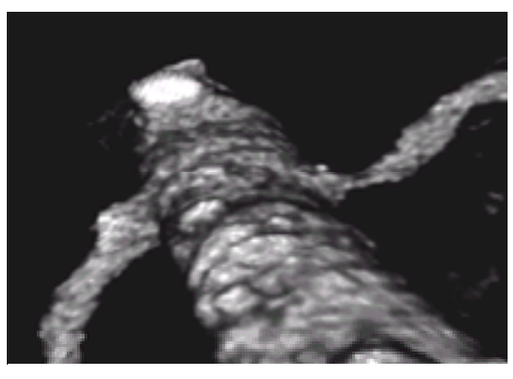


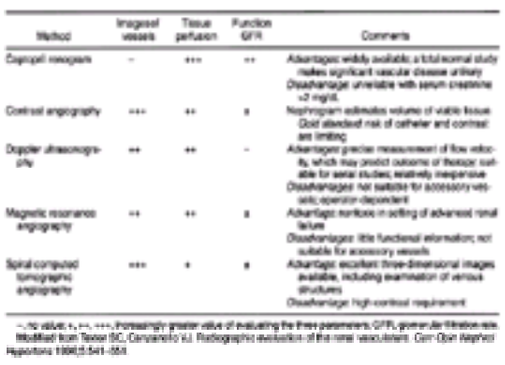
FIG. 10-7. An upward view of a spiral computed tomographic angiogram demonstrating proximal left renal artery atherosclerotic stenosis.

MRA has been improved by use of fast, breath-hold, three-dimensional gadolinium enhancement (De Cobelli et al., 2000). Thereby, accessory renal arteries can be visualized (Korst et al., 2000). Pedersen (2000) nonetheless states that “spiral CT [computed tomographic] angiography or conventional angiography is often prudent if one suspects stenosis of a branch renal artery or one or more accessory or aberrant arteries.” Gadolinium-enhanced MRA is particularly useful in patients with renal insufficiency, because it avoids the potential nephrotoxicity of contrast medium.

In an analysis of all data published before August 2000, Vasbinder et al. (2001) found that both computed tomographic and gadolinium-enhanced three-dimensional MRA were significantly more accurate than ultrasound or scintigraphy.

Choice of Procedures

Table 10-7 summarizes the different procedures available for evaluation of the renal vasculature (Safian and Textor, 2001; Textor and Canzanello, 1996). Captopril renography is included because it provides indirect evidence for a vascular lesion.



Method	Imaged vessels	Tissue perfusion	Function GFR	Comments
Captopril renogram	–	+++	++	Advantages: widely available; a total normal study makes significant vascular disease unlikely Disadvantage: unreliable with serum creatinine >2 mg/dL
Contrast angiography	+++	++	±	Nephrogram estimates volume of viable tissue Disadvantages: definite risk of catheter and contrast; ionizing
Doppler ultrasonography	++	++	–	Advantages: precise measurement of flow velocity, which may predict outcome of therapy; suitable for serial studies; relatively inexpensive Disadvantages: not suitable for accessory vessels; operator dependent
Magnetic resonance angiography	++	++	±	Advantages: nontoxic in setting of advanced renal failure Disadvantages: little functional information; not suitable for accessory vessels
Spiral computed tomographic angiography	+++	+	±	Advantages: excellent three-dimensional images available, including examination of venous structures Disadvantage: high contrast requirement

–, no value; +, ++, +++, increasingly greater value of evaluating the three parameters; GFR, glomerular filtration rate.
Modified from Textor SC, Canzanello VJ. Radiographic evaluation of the renal vasculature. Curr Opin Nephrol Hypertens 1996;5:541–551.

TABLE 10-7. *Relative strengths of selected methods of evaluating the renal vasculature*

The guidelines recommended by Pedersen (2000) seem appropriate:

> Tests for screening and diagnosing renal artery stenosis should be performed in patients with a high or moderate likelihood of having the disease according to the criteria previously discussed. In patients with normal renal function, the first test should be ACEI renography, conventional renography, or color Doppler sonography. The choice of the test depends on local experience and equipment. . . . If the test is positive, some kind of renal imaging must be performed. Spiral CT angiography or MRA are the best choices. Spiral CT angiography is superior to MRA in detecting accessory arteries and abnormalities in the distal part of the renal artery. If one's suspicion focuses on an atherosclerotic renal artery disease, the lesion will likely be in the proximal part of the artery, and MRA has sufficiently high accuracy. Conventional renal angiography would not be necessary.
>
> In patients with mild to moderate reduced renal function, that is, serum creatinine less than 200 µmol/L (~2.3 mg/dL), the same initial test can be used, either renography or color Doppler sonography. However, for imaging the renal arteries, MRA is preferred over spiral CT angiography to avoid the risk of nephrotoxicity.
>
> In patients with severe impairment in renal function, neither renography nor color Doppler sonography offers substantial assistance in diagnosing a renal artery stenosis. Magnetic resonance angiography is recommended. If MR scanning is not available, either spiral CT angiography or conventional angiography must be done, although both carry a calculated risk of nephrotoxicity.

THERAPY

Once a lesion is found and proved to be functionally significant, three choices are available for the treatment of RVHT: medical therapy, angioplasty, and surgical revascularization.

Medical Therapy

Although all classes of antihypertensive drugs have been used to treat RVHT, the most effective therapy is an ACEI (Losito et al., 1999). In the largest published analysis, captopril was effective for at least 3 months in more than 80% of 269 patients with RVHT; progressive renal failure mandating the discontinuation of therapy occurred in only 5% (Hollenberg, 1988).

As noted earlier, the use of an ACEI or ARB may markedly decrease blood flow to the kidney beyond the stenosis and, if that is the only kidney or if there is bilateral renovascular disease, the result may be rapid, although usually reversible, renal failure. This is not unique to ACEIs (Textor et al., 1985) but is more likely to occur with their use because of their greater effectiveness, the removal of angiotensin II support of autoregulation, and the preferential dilation of renal efferent vessels that together lead to reduced glomerular filtration and renal perfusion (van de Ven et al., 1998). Fortunately, return of renal function is usual when the ACEI is stopped. Nonetheless, complete occlusions of markedly stenotic renal arteries after ACEI therapy have been seen, particularly if the ACEI is given with a diuretic (Dussol et al., 1994).

Calcium channel blockers may provide equal control of hypertension and less impairment of renal function than do ACEIs, as they maintain blood flow better because of their preferential preglomerular vasodilative effect.

Caution is obviously needed in treating those with bilateral RVHT. Even without ACEIs, progression to end-stage renal disease may occur, particularly if the BP is not well controlled (Baboolal et al., 1998).

Angioplasty

Results

Since the first report of successful treatment of RVHT by percutaneous transluminal renal angioplasty (Grüntzig et al., 1978), fairly extensive experience has been reported and the technical aspects have continually improved. However, restenosis occurs within a year in at least one-fourth of patients after a first successful angioplasty, particularly in those with ostial lesions in association with severe aortic atherosclerosis. Better results are being reported with with transluminal stenting, increasingly per-formed as the initial procedure (Lederman et al., 2001; Leertower et al., 2000). Good results have also been seen in patients with ostial lesions (Beutler et al., 2000).

Complications

Complications occur in approximately 10% of patients; the rate and severity almost always decrease with increasing experience. Because the balloon causes cracking and occasional separation of the intima from the media rather than compression of atherosclerotic plaques, it is remarkable that so few complications have been observed. Rupture of the renal artery may occur as long as 9 days after the procedure (Olin and Wholey, 1987), but serious complications are relatively rare. However, the ready availability of surgical backup for possible serious complications is considered mandatory before angioplasty is performed.

Surgery

As surgery is being done on older and sicker patients, the results might be expected to be less impressive. Nonetheless, in multiple large series from major centers of

vascular surgery, results seem to be as good in the 1990s as they were in the 1980s (Aurell and Jensen, 1997; Textor, 1998).

These series report overall benefit (cured or improved) in 80% to 90% of patients operated on for atherosclerotic RVHT, with perioperative mortality being less than 5%. Comparisons between published series are likely inappropriate because multiple factors vary, including the type of patients, the need for additional surgery beyond the renal artery, and the length of follow-up. Moreover, the generally excellent results reported from such centers may not be shared by surgeons with less experience. On the other hand, more difficult patients are more likely referred to large centers. In all series, better results are noted in patients without renal insufficiency. Nonetheless, in 596 azotemic patients with RVHT reported in nine publications from 1987 to 1995, surgical revascularization achieved improved or stabilized renal function in 82% over a mean follow-up of 35 months, with a 5.2% mortality (Aurell and Jensen, 1997). During this same interval, 383 azotemic patients reported in eight publications achieved only a 64% improved or stabilized status by angioplasty over a mean follow-up of only 11 months (Aurell and Jensen, 1997).

As more patients with advanced atherosclerotic vascular disease in multiple organs are brought to surgery, repair of coronary or carotid disease may be performed either before (Cambria et al., 1995) or at the same time (Vivekananthan et al., 2000) as repair of the renal artery.

Results in Special Groups

Children

RVHT is second only to coarctation as a surgically remediable form of hypertension among children. Results of surgical repair generally have been good. Cure or improvement was reported in 27 of 28 treated with surgery from 1978 to 1988 by Martinez et al. (1990).

Nonfunctioning Kidneys

Even after complete occlusion of the renal artery, revascularization may be successful, even if delayed for as long as 56 days (Libertino et al., 1980). Patients who suddenly become anuric should be considered for immediate angiography, and if a correctable vascular lesion is identified, revascularization should be performed (Williams et al., 1988). Nephrectomy may be needed if repair is not feasible or if the kidney is nonfunctioning (Geyskes et al., 1987).

Arterial Stenosis after Transplantation

As discussed in Chapter 9, stenosis is one of the more common causes of posttransplantation hypertension. Operative intervention may be indicated, although angioplasty will usually be the first choice (Agroyannis et al., 2001).

Renal Embolization

In a few instances, percutaneous renal embolization by injection of ethanol into the renal artery has been successfully used to treat severe hypertension in patients with RVHT in whom neither surgery nor angioplasty was feasible and in whom medical therapy was unsuccessful (Iaccarino et al., 1989).

Choice of Therapy

In reviewing the recent literature, a number of points become obvious.

- There are no properly controlled, large-scale, long-term studies of the relative value of the three modes of therapy. A multicenter, randomized trial comparing renal artery stenting to aggressive medical therapy for preserving renal function is being organized (Safian and Textor, 2001).
- Patients with fibroplastic disease do better than do those with atherosclerotic disease when treated medically or by revascularization (Safian and Textor, 2001). Their better response likely reflects their younger age, less prolonged hypertension, and less atherosclerosis in other organs.
- For atherosclerotic RVHT, *medical therapy*, usually with an ACEI or ARB and often with a calcium channel blocker, may be effective over many years (Chábová et al., 2000), particularly with unilateral RVHT (Losito et al., 1999).
- *Angioplasty*, usually with a stent (Leertouwer et al., 2000), has become the initial therapy in most patients who do not tolerate or respond to medical therapy or who have progressive renal impairment (Watson et al., 2000), even with a solitary kidney (Shannon et al., 1998).
- *Surgical revascularization* is less commonly indicated, except when angioplasty with stenting is not feasible or is unsuccessful or when abdominal vascular surgery is required (McLaughlin et al., 2000). Nonetheless, in experienced hands, surgery provides equal, if not better, preservation of renal function and amelioration of hypertension as compared to other procedures (Krishnamurthi et al., 1999; Textor, 1998). Revascularization is preferable to nephrectomy in patients with chronic atherosclerotic renal artery occlusion if the distal portion is normal (Oskin et al., 1999).
- Combined intervention on both atherosclerotic coronary and renal arteries may be safe and beneficial (Vivekananthan et al., 2000).
- Revascularization or angioplasty is being increasingly performed for ischemic nephropathy, even in older patients with significant renal insufficiency (Dangas et al., 2000) or who are on dialysis for ESRD (Hansen et al., 1995). The recognition that as many as 20% of all patients with ESRD entering dialysis have renovascular disease, first demonstrated by Ying et al. (1984) and amply confirmed since then (Mailloux et al., 1994), is perhaps the most important recent advance in the arena of RVHT.

In the absence of large, controlled clinical trials comparing all available therapies, an individualized approach is recommended.

In their review, Safian and Textor (2001) recommend the approach shown in Figure 10-8, based on clinical characteristics, risk factors, baseline renal function, and the degree of asymmetry on nuclear imaging, with the primary goal of preserving renal function.

FIG. 10-8. Algorithm for evaluating patients in whom renal artery stenosis is suspected. Clinical follow-up includes periodic reassessment with duplex ultrasonography, magnetic resonance angiography, and nuclear imaging to estimate fractional blood flow to each kidney. The treatment of risk factors includes smoking cessation and the use of aspirin, lipid-lowering agents, and antihypertensive therapy. (Modified from Safian RD, Textor SC. Renal-artery stenosis. *N Engl J Med* 2001;344: 431–442.)

A similar approach is recommended by Block and Pickering (2000):

> Once the diagnosis of renal artery disease has been established, a careful risk-benefit analysis must be undertaken in each patient. This analysis should consider not only the patient's BP control and renal function, but also an assessment of overall mortality risk and the potential for morbidity from invasive procedures.
>
> . . . In each patient, the first task is to compare the likelihood of success with the risks of intervention. In patients who have a high likelihood of success and a low risk of complications, such as the majority of patients with fibromuscular disease and many patients with uncomplicated atherosclerotic RVHT, it is usually reasonable to proceed directly to revascularization by either PTRA [percutaneous transluminal renal angioplasty], stent placement, or surgery. In patients with fibromuscular disease and nonostial atherosclerotic disease, an attempt at routine PTRA is appropriate. For patients with ostial lesions or those who have a poor response to initial angioplasty, stent replacement should be considered. Medical management and close

surveillance remain important adjuncts in patients who have undergone percutaneous revascularization.

In many patients with atherosclerotic disease where the likelihood of success is less and the risk of complications is greater, it may be reasonable to proceed with a trial of medical management. Optimal medical management consists of aggressive BP control, lipid lowering agents, and antiplatelet therapy. In medically managed patients it is essential to carefully monitor for disease progression with serial serum creatinine and renal ultrasound or MRA. In patients whose BP is well controlled with medical management and who do not show progression of renal dysfunction or atrophy, it is usually appropriate to continue with medical management. However, in patients whose BP cannot be adequately controlled or who exhibit progression of clinical renal disease despite aggressive medical management, angioplasty or stent placement should be considered.

RENIN-SECRETING TUMORS

Renin-secreting tumors are not common, but clinicians should be aware that hypertension with a high renal venous renin level from one kidney may not always represent RVHT. Since the recognition of the first case of a renin-secreting tumor in 1967 (Robertson et al., 1967), more than 50 have been reported, and the syndrome has been well described (Corvol et al., 1994; Haab et al., 1995). Most such tumors are relatively small and are composed of renin-secreting juxtaglomerular cells (i.e., hemangiopericytomas). Other causes of hypertension and high renin levels include

- Wilms' tumor in children, usually associated with high levels of prorenin (Leckie et al., 1994).
- Renal cell carcinoma (Moein and Dehghani, 2000); tumors of various extrarenal sites, including lung, ovary, liver, pancreas, and sarcomas (Corvol et al., 1994), and adrenal paraganglionoma (Arver et al., 1999).
- Large intrarenal tumors that compress renal vessels.
- Unilateral juxtaglomerular cell hyperplasia (Kuchel et al., 1993).

Most of the renin-secreting tumors of renal origin fit a rather typical pattern:

- Severe hypertension in relatively young patients: The oldest reported has been 53 (Haab et al., 1995), but most are younger than 25.
- Very high prorenin and renin levels in the peripheral blood: Even higher levels are found from the kidney harboring the tumor (Koriyama et al., 1999).
- Secondary aldosteronism, usually manifested by hypokalemia.
- Tumor recognizable by computed tomographic scan.
- Tumor morphologically is a hemangiopericytoma arising from the juxtaglomerular apparatus.

Cure should be possible by removal of the tumor; if that is not possible, an ACEI or calcium channel blocker should be used.

Now that the renal causes of hypertension have been covered, we turn to those seen during pregnancy and with the use of oral contraceptives.

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11
Hypertension with Pregnancy and the Pill

Hypertension occurs in approximately 10% of first pregnancies and in as many as 3% of women who take oral contraceptives (OCs) for 5 years. In developed countries, and even more so in developing countries, hypertensive disorders of pregnancy are among the leading causes of maternal and perinatal mortality [National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (National HBPEP Working Group), 2000]. Moreover, the increasing evidence that low-birth-weight babies more likely develop hypertension in adult life (see Chapter 3) gives greater emphasis to the need for prevention of preeclampsia (PE) and prematurity as well as control of hypertension during pregnancy, as all three of these conditions are associated with low birth weight (Irving et al., 2000; Ødegård et al., 2000; Waugh et al., 2000).

Hypertension associated with the use of OCs may rapidly accelerate or may more slowly cause vascular damage. Although the causes of neither gestational nor pill-induced hypertension are completely known, if these forms of hypertension are recognized early and handled appropriately, the morbidity and mortality they cause can be largely prevented.

TYPES OF HYPERTENSION DURING PREGNANCY

As many as 5% of women enter pregnancy with preexisting hypertension (Ferrer et al., 2000); a larger number develop hypertension during pregnancy—as many as 10% of women in their first pregnancy (National HBPEP Working Group, 2000).

Classification

Although slightly different classifications may be used (Broughton Pipkin and Roberts, 2000; Walker, 2000), those provided in the 2000 report of the National HBPEP Working Group will be followed here:

- *Chronic hypertension:* hypertension, defined as a blood pressure (BP) in excess of 140 mm Hg systolic or 90 mm Hg diastolic (taken as the disappearance of sound or Korotkoff phase V), present before pregnancy or diagnosed before the twentieth week of gestation or that persists beyond 6 weeks postpartum.
- *Gestational hypertension* (GH; also called *pregnancy-induced hypertension*): hypertension detected for the first time after the twentieth week of gestation, without proteinuria. Some will develop PE; if not, and the BP returns to normal postpartum, the diagnosis of *transient hypertension of pregnancy* can be assigned; if the BP remains elevated postpartum, the diagnosis is *chronic hypertension*.
- *Preeclampsia:* hypertension detected for the first time after the twentieth week of gestation (or earlier with trophoblastic diseases) with proteinuria of at least 0.3 g in a 24-hour specimen.
- *Eclampsia:* PE with seizures that cannot be attributed to other causes. Seizures may be the first sign of PE (Katz et al., 2000).
- *PE superimposed on chronic hypertension:* in women with chronic hypertension, sudden increases of BP together with the appearance of proteinuria, thrombocytopenia, or abnormal liver function tests.

Problems in Diagnosing Preeclampsia

There are problems inherent in diagnosing a syndrome of unknown cause on the basis of only highly nonspecific signs (Higgins and de Swiet, 2001). For example, as will be noted, the BP in normal pregnancy usually falls during the first and middle trimester, only to return toward the prepregnant level during the third trimester. Because women with chronic hypertension have an even greater fall early on, their subsequent “normal” rise may give the appearance of the onset of PE. In addition, those with chronic hypertension may have previously unrecognized proteinuria: If seen only after midterm, the diagnosis of PE looks even more certain.

The distinction between chronic hypertension and PE is of more than academic interest: In the former, hypertension is the major problem, whereas “preeclampsia is more than hypertension; it is a systemic syndrome and several of its 'nonhypertensive' complications can be life-threatening when blood pressure elevations are quite mild” (National HBPEP Working Group, 2000). The management of the hypertension and the pregnancy, as well as the prognosis for future pregnancies, varies with the diagnosis. The bottom line, however, is clear: When in doubt, diagnose PE and institute its treatment, because even mild PE may rapidly progress. If PE is correctly diagnosed and managed, the risks to both mother and baby can be largely overcome.

As will be noted later, there is an additional issue as to whether GH and PE are part of the same spectrum of disease. As Broughton Pipkin and Roberts (2000) state:

> GH at term is usually associated with normally-grown, or even slightly large, babies. . . . Conversely, nulliparous women with PE have a four-fold greater likelihood of delivering a baby small for its gestational age than do normotensive nullips. Saudan et al. (1998) reported that 15–25% of women diagnosed initially with GH went on to develop PE, the likelihood being greater the earlier in pregnancy the hypertension developed. It may simply be that later-onset GH does not have time to develop into PE. Conversely the other 85% of women may have different, benign disease. This latter possibility is supported by epidemiological observations that indicate a greater risk of recurrence and essential hypertension in later life for women with GH than those with PE. . . . If one imagines that GH may be a physiological mechanism to compensate for impaired utero-placental perfusion, and PE a pathological breakdown of such a system, then the different outcomes become more comprehensible. It certainly seems improbable that a condition should occur with such frequency (GH ~10% in first pregnancy) at such a physiologically important time of life if it were wholly malign.

BLOOD PRESSURE MONITORING DURING PREGNANCY

The previously noted problems in defining various types of hypertension during pregnancy are compounded by problems of measuring BP. The various guidelines described in Chapter 2 should be followed in measuring the BP during pregnancy. For the diastolic level, the disappearance of sound (phase 5) is more accurate, reliable, and more easily ascertained than its muffling (phase 4) (Higgins and de Swiet, 2001).

Home Blood Pressure Recording

Patients may monitor their own BP with the semiautomatic, inexpensive devices described in Chapter 2 (Ross-McGill et al., 2000). If close observation is needed, the readings can be transmitted by computer (Naef et al., 1998).

Ambulatory Blood Pressure Monitoring

With ambulatory BP monitoring (ABPM) devices, 24-hour BPs have now been recorded in large numbers of normal and preeclamptic pregnancies. In normal pregnancy, lower pressures are found in the midportion, with rises to nonpregnant levels near term (Brown et al., 1998; Ferguson et al., 1994) (Fig. 11-1). Ambulatory measurements had a greater sensitivity (but lower specificity) than conventional sphygmomanometry for predicting progression to more severe hypertension within 2 weeks in pregnant women whose clinic BP was greater than 140/90 mm Hg (Penny et al., 1998).

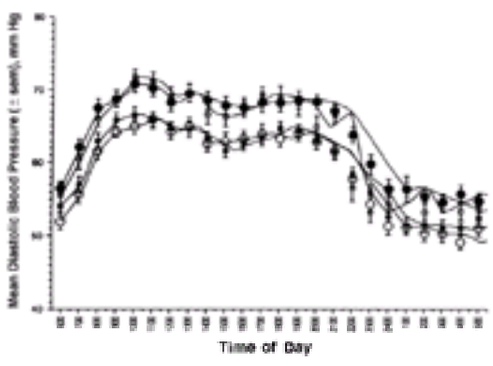


FIG. 11-1. Diastolic blood pressure patterns recorded hourly during three different gestational periods and in nonpregnant women. Mean diastolic blood pressure (± sem) was recorded in millimeters of mercury. Open squares with dot, nonpregnant; open circles, 18–22 weeks pregnant; solid squares, 30–32 weeks pregnant; solid circles, 36–38 weeks pregnant. (Reprinted from Ferguson JH, Neubauer BL, Shaar CJ. Ambulatory blood pressure monitoring during pregnancy. Establishment of standards of normalcy. *Am J Hypertens* 1994;7:838–843, with permission.)

Prospective Data

These data were from single sets of ABPM measurements in a cross-sectional study. Even more impressive are data from a longitudinal, prospective study in 202 women who started with normal casual BP (mean, 120/65 mm Hg) during the first trimester and who had repeated ABPM recordings made every 4 weeks (Hermida et al., 2000a). A highly significant higher level of both daytime and sleep BPs was noted *during the first trimester* in the 55 women who later developed GH and the 23 who later developed PE, in comparison to the 124 who remained normotensive. These data suggest that ABPM may provide the best tool now available for the early identification of women who are predisposed to GH or PE. Moreover, those who developed PE had a greater blunting of the nighttime dipping of BP during the third trimester as compared to those who only had GH, so the procedure may provide additional warning of the impending development of PE. Obviously, more such careful study of ABPM during pregnancy is needed.

White-Coat Hypertension

With ABPM, controversy as to the prevalence and significance of white-coat hypertension (WCH) during pregnancy has arisen, likely because different diagnostic criteria have been used with too few women studied at different times of gestation. Whereas some find WCH to be common [29% of 144 women during the third trimester (Bellomo et al., 1999)], others find it to be uncommon (4% of 121 women during the second half of pregnancy) (Brown et al., 1999). Some find those with WCH to have no difference in maternal or fetal outcomes as compared to those with similarly elevated BP in clinic and by ABPM (Brown et al., 1999); others find those with WCH to have far less progression to PE and fewer low-birth-weight babies, with out-comes little different from normotensive pregnant women (Bar et al., 1999; Bellomo et al., 1999). Obviously, more data are needed.

Current Practice

Until (and if) at-home BP monitoring and ABPM become widely available and further documented to be more predictive than office BPs, most women will be monitored by occasional readings in the office. The definitions given earlier in this chapter are based on office readings with the caveat that, unless the woman is in serious trouble, repeated readings be taken before diagnosing any form of hypertension.

With office readings, the diagnosis of hypertension either without proteinuria (i.e., gestational hypertension) or with proteinuria (i.e., PE) was clearly associated with significantly increased risks of maternal and fetal complications (North et al., 1999). Those women whose BP rose even more than 30/15 mm Hg but whose BP remained below 140/90 mm Hg had uncomplicated pregnancies. In another 90 women whose diastolic BP rose 15 mm Hg or more but remained below 90 mm Hg and who had proteinuria, there was no increase in adverse perinatal outcomes (Levine, 2000). Casual readings are clearly meaningful.

CIRCULATORY CHANGES IN NORMAL PREGNANCY

Many of the adaptations of normal pregnancy are amplifications of changes that occur in the luteal phase of every menstrual cycle (Brough-ton Pipkin and Roberts, 2000). As Broughton Pipkin and Roberts (2000) note, “These changes are all amplified should conception occur. They are thus proactive, not reactive.”

Serial measurements begun even before conception (Chapman et al., 1998) or soon thereafter (Poppas et al., 1997) have portrayed the evolution of the profound changes of normal pregnancy.

Hemodynamic Changes

In the ten women, nine nulliparous, who were studied before and repeatedly during pregnancy beginning before 6 weeks' gestation, significant decreases in systemic vascular resistance resulted in a fall in BP, despite an increase in cardiac output, even before placentation (Chap-man et al., 1998) (Fig. 11-2). As the authors note, “Therefore, it is likely that maternal factors, possibly related to changes in ovarian function or extended function of the corpora lutea, are responsible for the initial

peripheral vasodilation found in human pregnancy” (Chapman et al., 1998).

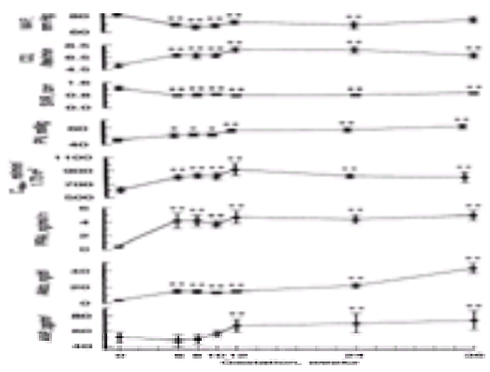


FIG. 11-2. Changes in mean arterial pressure (MAP), cardiac output (CO), systemic vascular resistance (SVR), plasma volume (PV), effective renal plasma flow measured by para-aminohippurate clearance (C_{PAH}), plasma renin activity (PRA), plasma aldosterone (Aldo), and atrial natriuretic peptide (ANP) in ten women studied in the midfollicular phase of the menstrual cycles and at weeks 6, 8, 10, 12, 24, and 36 of gestation. * *p* <.05; ***p* <.01. (Reprinted from Chapman AB, Abraham WT, Zamudio S, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int* 1998;54:2056– 2063, with permission.)

The progressive rise in plasma and blood volume are likely adaptations, via renal sodium retention, to the vasodilation and fall in BP. The low pressure and underfilled circulation provoke an increase in renin secretion and, secondarily, a rise in aldosterone levels. The somewhat later rise in plasma atrial natriuretic peptide is evidence that, despite the increased blood volume, the central circulation is not overexpanded.

As a consequence of renal vasodilation, renal plasma flow and glomerular filtration increase and renal vascular resistance decreases. As Chapman et al. (1998) state: “The hormonal changes associated with pregnancy have a specific renal vasodilating effect, overriding secondary activation of other renal vasoconstricting systems such as the renin-angiotensin system.”

Hormonal Changes

Renin-Angiotensin-Aldosterone

Active and inactive plasma renin levels and renin substrate are increased in normal pregnancy (Brown et al., 1963). The levels of renin activity and concentration are elevated in part as a consequence of the estrogen-induced stimulation of renin substrate, which increases nearly sixfold (Sealey et al., 1994). Two other factors contribute to the rise in renin: the various hemodynamic and renal changes described earlier, which activate the release of renin, which in turn helps maintain BP (August et al., 1995), and the contribution of renin synthesized in the placenta (Li et al., 2000).

Prorenin, the biosynthetic precursor of renin, is produced in large amounts early in pregnancy in the ovaries and later in the uteroplacental unit, but its function remains unclear (Itskovitz et al., 1992).

At the same time as various forces raise levels of renin-angiotensin-aldosterone, normal pregnancy brings forth numerous mechanisms to protect the circulations of both mother and fetus from the intense vasoconstriction, volume retention, and potassium wastage that high angiotensin II and aldosterone levels would ordinarily engender.

Responsiveness to Angiotensin and Aldosterone

Pregnant women are relatively resistant to the pressor effects of exogenous angiotensin II (Abdul-Karim and Assali, 1961; Ito et al., 1992); this reflects downregulation of angiotensin II receptors by the high levels of circulating angiotensin II (Baker et al., 1992) and antagonism by endothelium-derived prostacyclin and nitric oxide (NO), which are vasodilative (Magness et al., 1996). Moreover, the placenta is less responsive to angiotensin II than are most nonreproductive tissues, which results in a preferential maintenance of perfusion through the uteroplacental bed (Cox et al., 1996).

The large amounts of potent mineralocorticoids present during pregnancy would be expected to increase sodium reabsorption at the cost of progressive renal wastage of potassium, yet pregnant women are normokalemic. This appears to be the result of the high level of progesterone, which acts as an aldosterone antagonist (Brown et al., 1986).

Prostaglandin Synthesis

As noted, the resistance to angiotensin has been thought to involve the increased synthesis of vasodilative prostanoids, as reflected by progressively higher plasma levels of prostacyclin and lower levels of thromboxane during normal pregnancy (Klockenbusch et al., 1994). However, serial measurements of circulating concentrations of thromboxane A_2 and prostacyclin in 160 women found no significant differences through normal or hypertensive pregnancy and no relation of their concentration to venous distensibility (Smith et al., 1995).

Overview of the Circulation in Normal Pregnancy

Normal pregnancy, then, is a low BP state associated with marked vasodilation that reduces peripheral resistance, along with an expanded fluid volume that increases cardiac output. Renal blood flow is markedly increased, and the renin-aldosterone system is activated but with blunted effects.

PREECLAMPSIA

All of the preceding is a prologue to our understanding of PE. Almost all these various hemodynamic, renal, and hormonal changes of normal pregnancy are altered in PE.

PE is a systemic syndrome of which hypertension is only its most obvious manifestation. As noted in the preamble to the report of the National HBPEP Working Group (2000):

> The maternal disease is characterized by vasospasm, activation of the coagulation system, and perturbations in many humoral and autacoid systems related to volume and BP control. Oxidative stress and inflammatory-like responses may also be important in the pathophysiology of preeclampsia. The pathologic changes in this disorder are primarily ischemic in nature and affect the placenta, kidney, liver, and brain.

Marked changes in hemodynamics occur: The previously elevated cardiac output plummets; the reduced peripheral resistance markedly rises (Bosio et al., 1999). Blood volume shrinks (Silver et al., 1998), presumably reflecting the vasoconstricted vasculature. Adaptation to the elevated BP by the heart leads to increases in left ventricular mass and end-systolic and -diastolic volumes with reductions in left ventricular ejection fraction (Borghi et al., 2000). These changes are paralleled by increases in plasma levels of atrial and brain natriuretic peptides, which reflect ventricular overload.

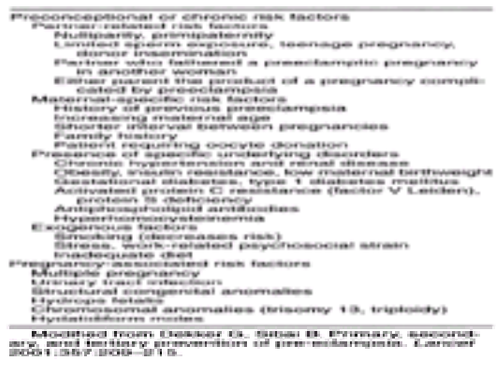
In addition to other features that are described in the later section, Consequences, a distinctive renal glomerular lesion is seen (Gärtner et al., 1998). As long noted, women who develop PE before 30 weeks' gestation are more likely to have preexisting renal disease (Murakami et al., 2000).

Pathogenesis

The cause of PE must explain the following features, as delineated by Chesley (1985):

- It occurs almost exclusively during the first pregnancy; nulliparas are six to eight times more susceptible than are multiparas.
- It occurs more frequently in the young and in those with multiple fetuses, hydatidiform mole, or diabetes.
- The incidence increases as term approaches; it is unusual before the end of the second trimester.
- The features of the syndrome are hypertension, edema, proteinuria and, when advanced, convulsions and coma.
- There is characteristic renal and hepatic pathology.
- The syndrome has a hereditary tendency; in the families of women who had PE, the syndrome developed in 25% of their daughters and granddaughters but in only 6% of their daughters-in-law (Chesley, 1980).
- It rapidly disappears when the pregnancy is terminated.

As listed in Table 11-1, multiple risk factors for PE have been identified (Dekker and Sibai, 2001). Its often erratic course has been well studied, and many of the mechanisms for various consequences are known. What remains elusive is the initiating mechanism, the trigger that sets off the oftentimes explosive course of this strange malady that disturbs up to one in ten first pregnancies and is hardly ever seen again. The difficulty in identifying a specific cause may be related to the presence of multiple mechanisms (Roberts and Cooper, 2001).



Modified from Dekker G, Sibai B: Primary, secondary, and tertiary prevention of pre-eclampsia. Lancet 2001;357:209–215.

TABLE 11-1. *Risk factors for preeclampsia*

One of the major difficulties in finding the initiating mechanism is the lack of an experimental model for PE. All that we know must be derived from studies in humans, hard enough in the non-pregnant but even more difficult during pregnancy. As noted by Broughton Pipkin (1995): “We are confined . . . to studies of blood samples and trophoblast obtained at chorion villus sampling and to such monitoring as Doppler ultrasonography that are safe during repeated use.”

Another difficulty is the inability to identify the early pathogenetic mechanisms, which remain invisible to current technology. Most of what is recognized are late manifestations of a process that is initiated much earlier. Attention must be paid to these manifestations, but they are likely epiphenomena, of little or no relevance to cause.

Genetic Predisposition

As noted by Chesley (1985), there is a genetic predisposition to PE. In the words of Broughton Pipkin and Roberts (2000):

> Rather than a single gene, there are likely the combined effects of several polymorphisms, probably in several different combinations, interacting with their environment and eventually precipitating a final common pathway of hypertension and proteinuria.

A number of candidate genes have been proposed, including ones associated with thrombophilias (Kupferminc et al., 1999), factor V Leiden mutation (Dizon-Townson et al., 1996), tumor necrosis factor–a (Williams et al., 1999), angiotensinogen (Morgan et al., 1999), and lipoprotein-lipase (Hubel et al., 1999).

All of these searches have involved small samples of women with varying features of PE. With newly available genotyping technology, larger and wider searches will hopefully identify those genes that are relevant to the predisposition to PE (Esplin et al., 2001).

Immunologic Mechanisms

A number of associations suggest an immunologic mechanism that involves the duration and degree of exposure to antigens in the father's sperm. Women who develop PE tend to have had shorter durations of cohabitation than women who do not have hypertension during pregnancy, suggesting that repeated exposure to male ejaculate may prevent PE (Robillard and Hulsey, 1996). Similarly, the risk is greater for former users of contraceptives that block exposure to sperm (Klonoff-Cohen et al., 1989). In addition, the risk of PE is reduced among women with prior miscarriages, abortion (Eras et al., 2000), or previous blood trans-fusions, all of which may alter maternal immune reactions (Clark, 1994).

These associations suggest that repeated exposure to sperm may correct a defect in trophoblast invasion, as will be described in the next section. As stated by Roberts (2000): “The increased frequency of preeclampsia in first pregnancy is secondary to immunologically mediated abnormal implantation resulting in reduced placental perfusion. This defect is 'cured' by paternal antigen exposure during the first pregnancy.”

Pathophysiology

Whatever is fundamentally responsible, as stated by Walker (2000): “Preeclampsia is the result of an initial placental trigger, which has no adverse effect on the mother, and a maternal systemic reaction that produces the clinical signs and symptoms of the disorder.”

Deficient Trophoblastic Migration

The current leading hypothesis for the placental trigger is poor placental perfusion, first proposed more than 50 years ago (Page, 1948) but now related to deficient trophoblastic migration and invasion (Clausen et al., 2000). As noted by Redman and Sargent (2000):

> It is now taken for granted that pre-eclampsia originates with deficient placentation occurring during the first half of pregnancy. The critical process is invasion of the placental bed by extravillous cytotrophoblasts, which penetrate deep into the myometrium. They also infiltrate the spiral arteries, which are transformed into large structureless conduits, which can supply the hugely expanded blood flow of the third-trimester placenta [Fig. 11-3]. In pre-eclampsia, cytotrophoblast invasion is abnormally shallow, so that only the decidual segments of the spiral arteries are modified and the distal myometrial segments remain small and muscular.

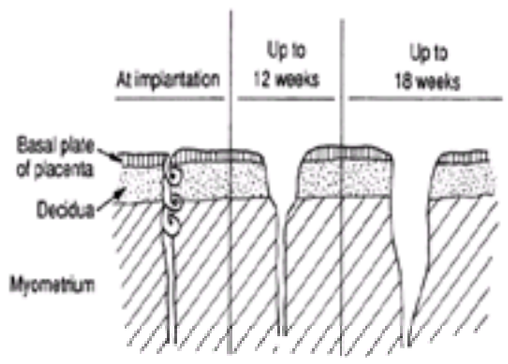


FIG. 11-3. The normal invasion of spiral arteries by the trophoblast converts them into deltas and so improves blood flow. This invasion is defective in preeclampsia. (Reprinted from Chamber-lain G. Raised blood pressure in pregnancy. *BMJ* 1991;302:1454–1458, with permission.)

Uteroplacental Hypoperfusion

The consequences of deficient trophoblastic migration with retention of musculoelastic media in spiral arteries could explain the major phenomenon that is usually held responsible for the pathophysiology of PE: uteroplacental hypoperfusion. Uteroplacental hypoperfusion fits with the recognized clinical circumstances wherein PE is most common: *reduced placental mass relative to need* (first pregnancies in young women, twins, hydatidiform mole) and *compromised uterine vasculature* (diabetes and preexisting hypertension).

As attractive as this theory is, it may not be the primary or sole mechanism. As Redman and Sargent (2000) note, not all PE is associated with fetal growth impairment as would be expected with impaired placentation and uteroplacental hypoperfusion; conversely, restricted placentation is seen in some pregnancies with small babies but without PE.

Redman et al. (1999) therefore propose:

> . . . that poor placentation should be classified as a separate problem which powerfully predisposes to, but is not the same as, pre-eclampsia. Early onset pre-eclampsia, which is most associated with fetal growth impairment, is likely to be the end point of poor placentation when it causes a maternal syndrome. Some women, probably because of their inheritance, may not be susceptible to pre-eclampsia and therefore show only the fetal part of the syndrome of poor placentation, namely poor growth. Ness and Roberts (1996) have put forward a related hypothesis, namely that pre-eclampsia may be 'placental,' caused by poor perfusion, or 'maternal,' being the result of a maternal pre-disposition to arterial disease, later expressed in longer term problems such as atherosclerosis or chronic hypertension.

This maternal predisposition to arterial disease has been identified as *acute atherosis*, an obstructive lesion of the spiral arteries, which could reduce placental perfusion even in the absence of poor placentation.

Endothelial Dysfunction

Redman and Sargent (2000) proceed to incorporate the proposal by Roberts et al. (1989) that the maternal features of PE are secondary to diffuse endothelial cell dysfunction. Some women are more sensitive to endothelial dysfunction or have preexisting dysfunction secondary to hypertension or diabetes; such dysfunction is one aspect of a generalized systemic maternal inflammatory response. As Redman and Sargent (2000) state:

> . . . this inflammatory response is detected in normal pregnancy when it is not intrinsically different from that in pre-eclampsia except that it is milder. We have proposed that pre-eclampsia develops when the systemic inflammatory process causes one or other maternal system to decompensate. In other words, the disorder is not a separate condition but simply the extreme end of a range of maternal systemic inflammatory responses engendered by pregnancy itself. This, the continuum theory of pre-eclampsia, implies that any factor that would increase the maternal system inflammatory response to pregnancy would predispose to pre-eclampsia. There are three possible such factors, and there is evidence that all are relevant: a large placenta; an abnormal stimulus from a small placenta; or an excessive maternal sensitivity to such stimuli [Fig. 11-4].

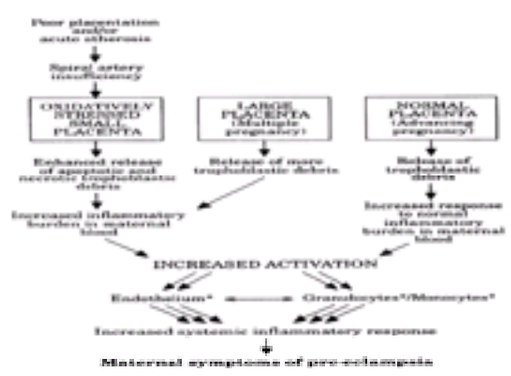


FIG. 11-4. Redman-Sargent model for the maternal symptoms of preeclampsia based on the release of trophoblastic debris into the maternal circulation. *, Activated cells. (Reprinted from Redman CWG, Sargent IL. Placental debris, oxidative stress and pre-eclampsia. *Placenta* 2000;21:597–602, with permission.)

Inflammatory Stimulus

As seen in Figure 11-4, the release of trophoblastic debris into the maternal circulation is considered to be the most likely stimulus for the inflammatory response of PE (Knight et al., 1998). Other stimuli have been proposed, including agonistic autoantibodies against the angiotensin AT $_1$receptor (Wallukat et al., 1999), which cause vascular cells to express tissue factor (Dechend et al., 2000), placental vascular endothelial growth factor (Simmons et al., 2000), neurokinin B (Page et al., 2000), free fatty acids (Endresen et al., 1998), other inhibitors of endothelium-dependent relaxation in plasma from women with PE (Hayman et al., 2000), and inflammatory cytokines which do arise from the placenta (Benyo et al., 2001).

In addition, a failure of NO release in response to shear stress in myometrial arteries from women with PE has been reported (Kublickiene et al., 2000). Inhibitors of NO release, including peroxynitrite, could be released in reaction to oxidative stress (Roggensack et al., 1999). The reduction in flow-mediated vasodilation in women with PE has been observed in peripheral arteries and was negatively correlated with levels of plasma fibronectin, a marker of endothelial cell injury (Yoshida et al., 2000).

The impairment in vasodilation could also explain the increased pressor responsiveness to exogenous angiotensin II seen as early as the twenty-second week of gestation, often 10 to 15 weeks before hypertension appears (Gant et al., 1973).

Redman and Sargent (2000) conclude their proposed scheme by invoking:

> . . . release of a steady stream of placental debris into the maternal circulation that provokes a systemic inflammatory response in all women, which is exaggerated if the burden of the debris is abnormally high or if the woman responds excessively. . . . Oxidative stress in the placenta leads to an overload of debris by stimulating apoptosis or necrosis or both. Such stress is most likely from spiral artery disease either from deficient placentation or acute atherosis.

In keeping with the putative role of oxidative stress as “the linkage between decreased placental perfusion and the maternal syndrome” (Roberts and Cooper, 2001), supplementation with antioxidants (vitamins C and E) to women at high risk of PE reduced the development of the disease by 71% as compared to the rate in those

given placebo (Chappell et al., 1999). However, the 11 women who developed PE in the vitamin group had a worse perinatal outcome than did the 24 in the control group.

As attractive as this model is, it is only the latest in a long progression of theories to explain PE.

Prostaglandins

One possible contributor to PE is an imbalance between vasodilating (prostacyclin) and vasoconstricting (thromboxane A_2) eicosanoids, originally proposed by Speroff in 1973. In a large prospective study, those women who developed PE had significantly lower urinary metabolites of prostacyclin at 13 to 16 weeks' gestation, long before the onset of clinical features (Mills et al., 1999). Levels of thromboxane A_2 metabolites were not increased, leading to a 24% higher ratio of vasoconstricting versus vasodilating effects.

A recently recognized group of prostaglandin-like compounds, isoprostanes, are produced by the action of free oxygen radicals on arachidonic acid bound to the phospholipid plasma membrane and released by the action of phospholipase A_2. Levels of 8-isoprostane were increased in the plasma of women with severe PE (McKinney et al., 2000), levels which remain elevated at 6 weeks postpartum (Barden et al., 2001).

Prevention with Low-Dose Aspirin

The belief that vasoconstricting thromboxanes were involved in the pathogenesis of PE prompted a number of trials of antiplatelet drugs, mostly low doses of aspirin, which preferentially block platelet synthesis of thromboxanes while sparing endothelial production of prostacyclin. In 32 trials of antiplatelet drugs, most with aspirin, involving more than 30,000 women, the risk of PE was reduced by 15% (95% confidence interval, 0.78–0.92) (Duley et al., 2001). Moreover, if given earlier in pregnancy and in larger doses later in the day, aspirin may be even more beneficial (Hermida et al., 2000b).

Associated Findings

A number of other associations—some possibly pathogenetic, others merely coincidental—have been reported. These include:

- A mutation in the mineralocorticoid receptor that alters the receptor specificity so that progesterone and other steroids lacking 21-hydroxyl groups (markedly elevated during pregnancy), which normally are mineralocorticoid receptor antagonists, become potent agonists (Geller et al., 2000). This autosomal dominant mutation was found in two women who had undergone five pregnancies, all complicated by marked exacerbation of hypertension.
- Increased level of endothelin-1 (Zafirovska et al., 1999).
- Increased levels of platelet-activating factor (Rowland et al., 2000).
- In addition to a marked increase in the incidence of PE in women with diabetes (Sibai et al., 2000), lesser increases in those with abnormal glucose tolerance or gestational diabetes (Joffe et al., 1998). This may relate to the greater risk in women who are overweight (Martin et al., 2000) or who are insulin-resistant (Solomon and Seely, 2001) and have features of the metabolic syndrome (Barden et al., 1999). As a consequence, they may have overly large babies (Xiong et al., 2000).
- Increased free leptin levels (Teppa et al., 2000).
- Increased job strain (Marcoux et al., 1999).
- Living at high altitude (Palmer et al., 1999).
- Long-time prior use of OCs (Thadhani et al., 1999).
- A history of low birth weight in the first pregnancy (Rasmussen et al., 2000).
- Lower body magnesium and plasma calcium but increased red blood cell membrane calcium (Kisters et al., 2000).
- Decreased 1,25-dihydroxyvitamin D levels, which could reduce plasma calcium, stimulate parathyroid hormone, and thereby increase distal renal tubular reabsorption of calcium, resulting in hypocalciuria (August et al., 1992).
- Marked alterations in sleep architecture (Edwards et al., 2000) and increased snoring (Franklin et al., 2000).

One apparent association goes against all the evidence that prior vascular injury increases the risk of PE—namely that women who smoke have a *lower* risk, even after they quit (Ros et al., 1998; Zhang et al., 1999). The association is not explained by their lower body weight.

An Overview

These factors and others may all play some role in the overall pathophysiology of PE, but impaired trophoblastic implantation, likely with some genetic component, remains the leading current hypothesis for the initiating mechanism (Granger et al., 2001).

The syndrome may represent a protective mechanism designed to preserve fetoplacental perfusion that goes awry. Broughton Pipkin (1995) suggested that reduced uteroplacental blood flow

> . . . stimulates the uteroplacental reninangiotensin system, which both increases peripheral vascular resistance and hence perfusion pressure directly and stimulates vasodilator synthesis within the pregnant uterus, allowing increased perfusion. The fact that the administration of angiotensin converting enzyme inhibitors to pregnant women lowers maternal blood pressure, but at cost to the fetus, supports this hypothesis.
>
> What then turns a protective mechanism into a rapidly worsening cascade of events? The fetus's absolute metabolic demands increase rapidly in the third trimester. . . . If hypoxia develops early or there is considerable endothelial damage, or both, then compensatory mechanisms may be unable to cope.

Manifestations of More Severe Disease

Intravascular Coagulation

As seen in Figure 11-5, activation of intravascular coagulation and subsequent fibrin deposition may be responsible for much of the eventual organ damage seen in severe PE. Increased plasma levels of indicators of platelet activation (b-thromboglobulin), coagulation (thrombin– antithrombin III complexes), and endothelial cell damage (fibronectin and laminin) have been measured up to 4 weeks before the onset of clinical features of PE, suggesting that these processes may be more involved than usually is credited (Ballegeer et al., 1992).

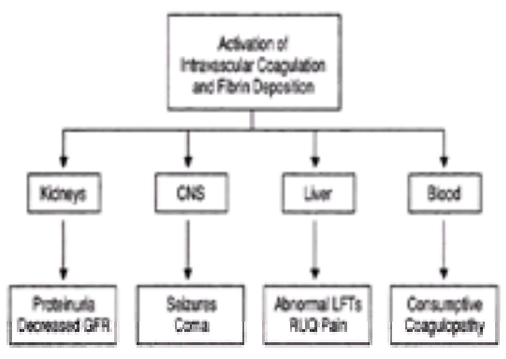


FIG. 11-5. Proposed model to explain the consequences of activation of intravascular coagulation and fibrin deposition in the pathophysiology of preeclampsia. CNS, central nervous system; GFR, glomerular filtration rate; LFT, liver function test; RUQ, right upper quadrant. (Reprinted from Friedman SA. Pre-eclampsia: a review of the role of prostaglandins. Obstet Gynecol 1988;71:122–137, with permission.)

Moreover, among 58 women with PE during their first pregnancy who were studied 5 months postpartum, 46% continued to have laboratory features of thrombophilia, most commonly anticardiolipin antibodies or antithrombin deficiency, suggesting that their PE may have been superimposed on a preexisting vascular clotting disorder (Spaanderman et al., 2000).

HELLP Syndrome

A few women develop a more serious complication of PE: the HELLP syndrome, which involves *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*late-let counts (Walker, 2000). The syndrome shares many features with the hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (Sibai et al., 1994). In one series of 454 pregnancies, with increasing degrees of thrombocytopenia of fewer than 150,000 platelets per mL, maternal and perinatal mortality increased and one in six patients developed eclampsia (Martin and Magann, 1996).

Cerebral Blood Flow

As will be noted, convulsions may occur (i.e., eclampsia) with or without prior manifestations of PE, suggesting that a continuum may or may not be in play. Many women with PE develop headaches; a few develop cortical blindness (Apollon et al., 2000) and other neurologic features of hypertensive encephalopathy. As described in Chapter 8, hypertensive encephalopathy reflects break-through hyperperfusion on the background of vasospasm. Similar findings have been described in PE: both vasospasm (Brackley et al., 2000) and brain edema (Schwartz et al., 2000) that reflects an increase in cerebral blood flow with a failure of autoregulation (Belfort et al., 1999), as well as endothelial damage (Schwartz et al., 2000).

Prevention

Dekker and Sibai (2001) have divided prevention into three stages:

1. *Primary* prevention will obviously be difficult without knowledge of the cause. However, avoidance of the known risk factors (Table 11-1) should help. In particular, avoiding teenage pregnancy, reducing obesity and insulin resistance, providing adequate nutrition, and avoiding multiple births during assisted pregnancies should be protective.
2. *Secondary* prevention involves identifying the syndrome as early as possible and using strategies that are thought to influence pathogenic mechanisms. These include low-dose aspirin, calcium supplementation, and fish-oil supplements. The latest updates from the Cochrane Library support the benefit of low-dose aspirin (Duley et al., 2001) and calcium supplements for women with low baseline calciumintake (Atallah et al., 2000). Fish-oil supple ments have been tested in six multicenter tri als and been found to reduce preterm delivery but not to affect any other outcomes (Olsen et al., 2000). In addition, correction of hyperho mocysteinemia and reduction of oxidative stress by antioxidants are being investigated.
3. *Tertiary* prevention involves the various lifestyle changes and therapies that will be described in the section Management.

Diagnosis

As described in the first section of this chapter, hypertension developing after the twentieth week of gestation with proteinuria in a young nullipara is probably PE, particularly if she has a positive family history for the syndrome. Because patients usually have no symptoms, prenatal care is crucial to detect the signs early and thereby prevent the dangerous sequelae of the fully developed syndrome. Unfortunately, such prenatal care may be increasingly unavailable for those most susceptible—young, uninsured, indigent women.

Early Detection

In keeping with the list of known risk factors (Table 11-1), young primigravidas and women with the following features should be more closely monitored: a family history of PE; multiple fetuses; black race; preexisting hypertension, heart disease, or renal disease; obesity, and PE in a previous pregnancy.

A number of clinical and laboratory tests have been used in an attempt to recognize PE before it develops and to differentiate it from primary hypertension. As Dekker and Sibai (2001) note: “No one test is truly predictive, though some tests are useful to detect patients at risk. The multifactorial origin of preeclampsia suggests that it is highly unlikely that there will be one universal predictive test in the future.”

Hypertension

The BP criterion is based on readings of 140/90 mm Hg or higher recorded on at least two occasions, 6 hours or more apart. Obviously, it is not possible to reconfirm the pressure levels over many weeks, as is recommended in nonpregnant patients.

The criteria of a rise of more than 30/15 mm Hg is no longer included, but such rises “warrant close observation, especially if proteinuria and hyperuricemia are also present” (National HBPEP Working Group, 2000).

Overdiagnosis

Despite the greater overall perinatal mortality with even transient elevations in pressure, for the individual patient there is a significant chance of overdiagnosing PE on the basis of these values, which have been found to have only a 23% to 33% positive predictive value and an 81% to 85% negative predictive value (Dekker and Sibai, 2001). Higher ambulatory BP and heart rate are present at 18 weeks' gestation in those who later developed PE; but those signs, too, have low predictive value (Brown et al., 2001). Therefore, multiple readings and careful follow-up over at least a few days or weeks are needed for women who display such findings in the absence of any other suggestive features before the clinician should make the diagnosis or institute therapy.

Consequences

On the other hand, the level of pressure may not be inordinately high for it to have serious consequences: Women may convulse because of hypertensive encephalopathy with pressures of only 160/110 mm Hg. As noted in the report of the National HBPEP Working Group (2000):

> The clinical spectrum of preeclampsia ranges from mild-to-severe forms. In most women, progression through this spectrum is slow, and the disorder may never proceed beyond mild preeclampsia. In others, the disease progresses more rapidly, changing from mild to severe in days or weeks. In the most serious cases, progression may be fulminant, with mild pre-eclampsia evolving to severe preeclampsia or eclampsia within days or even hours. Thus, for clinical management, preeclampsia should be overdiagnosed, because a major goal in managing preeclampsia is the prevention of maternal or perinatal morbidity and mortality, primarily through timing of delivery.

Proteinuria

Proteinuria is defined as more than 300 mg of protein in a 24-hour urine collection or 300 mg per L in two random, cleanly voided specimens collected at least 4 hours apart. The proteincreatinine ratio in a random urine sample accurately estimates proteinuria and likely can replace 24-hour collections (Sepandj et al., 1996). Even microalbuminuria early in the third trimester may predict subsequent PE (Bar et al., 1996).

Differential Diagnosis

Most women with typical features of *de novo* hypertension in pregnancy with no other obvious disorders turn out to have PE (Reiter et al., 1994). However, primary (essential) hypertension or chronic renal disease may be responsible, as has been identified by renal biopsy (Hill et al., 1988).

As described in the report of the National HBPEP Working Group (2000):

> Preeclampsia may occur in [15–25% of] women already hypertensive (i.e., who have chronic hypertension). . . . [T]he diagnosis of superimposed preeclampsia is highly likely with the

following findings:

- In women with hypertension and no proteinuria early in pregnancy (<20 weeks), new-onset proteinuria, defined as the urinary excretion of 0.3 g protein or greater in a 24-hour specimen.
- In women with hypertension and proteinuria before 20 weeks' gestation.
- Sudden increase in proteinuria.
- A sudden increase in BP in a woman whose hypertension has previously been well controlled.
- Thrombocytopenia (platelet count <100,000 cells per mm3).
- An increase in ALT [alanine aminotransferase] or AST [aspartate aminotransferase] to abnormal levels.

Management

The report of the National HBPEP Working Group (2000) provides these three tenets for management:

1. Delivery is always appropriate therapy for the mother but may not be so for the fetus. . . . The cornerstone of obstetric management of preeclampsia is based on whether the fetus is more likely to survive without significant neonatal complications *in utero* or in the nursery.
2. The pathophysiologic changes of severe preeclampsia indicate that poor perfusion is the major factor leading to maternal physiologic derangement and increased perinatal morbidity and mortality. Attempts to treat preeclampsia by natriuresis or by lowering blood pressure may exacerbate the important pathophysiologic changes.
3. The pathogenic changes of preeclampsia are present long before clinical diagnostic criteria are manifest. . . . These findings suggest that irreversible changes affecting fetal well-being may be present before the clinical diagnosis. If there is a rationale for management other than delivery, it would be to palliate the maternal condition to allow fetal maturation and cervical ripening.

Nonpharmacologic Management

Monitoring

After an initial in-hospital evaluation, highly motivated women who have mild GH or PE remote from term may be safely followed as outpatients if they are able to monitor their BP with home semiautomatic devices, weigh themselves, check fetal movements, and measure urinary protein (Barton et al., 1994). Barton et al. (1994) achieved similar maternal and perinatal outcomes as those reported with inpatient management, and at far less cost.

Modified Bed Rest

The value of bed rest has been widely accepted but has not been shown to be beneficial (Allen et al., 1999).

Diet

Current evidence favors maintenance of usual sodium intake to avoid further reducing placental perfusion (Knuist et al., 1998). Calcium supplements, although claimed to be effective for prevention of PE in high-risk populations, are not useful for therapy (DerSimonian and Levine, 1999). Because caffeine increases the risk of first-trimester abortion, it seems reasonable to restrict its intake even more in women with PE (Cnattingius et al., 2000).

Pharmacologic Therapy

The National HBPEP Working Group (2000) states:

> Antihypertensive therapy is indicated when blood pressure is dangerously high or rises suddenly in women with preeclampsia, especially intrapartum. Antihypertensive agents can be withheld as long as maternal pressure is only mildly elevated. Some experts would treat persistent diastolic levels of 105 mm Hg or higher. Others would withhold treatment until diastolic blood pressure levels reach 110 mm Hg. In adolescents whose diastolic pressures were recently below 75 mm Hg, treating persistent levels of 100 mm Hg or higher may be considered. When treatment is required, the ideal drug that reduces pressure to a safe level should act quickly, reduce pressure in a controlled manner, not lower cardiac output, reverse uteroplacental vascular constriction, and result in no adverse maternal or fetal effects. The medications used to treat hypertensive crises in pregnancy, and their route of administration, are summarized in [Table 11-2].

Drug[a]	Recommendations
Hydralazine	Start with 5 mg i.v. or 10 mg i.m. If BP is not controlled, repeat at 20-min intervals (5–10 mg depending on response). Once BP control has been achieved, repeat as needed (usually about 3 h). If no success with total of 20 mg i.v. or 30 mg i.m., consider another drug.
Labetalol	Start with 20 mg i.v. as a bolus; if effect is suboptimal, then give 40 mg 10 min later and 80 mg every 10 min for two additional doses. Use a maximum of 220 mg. If desired BP levels are not achieved, switch to another drug. Avoid giving labetalol to women with asthma or congestive heart failure.
Nifedipine	Start with 10 mg orally and repeat in 30 min if necessary. See text for precautions (under Treatment of Acute Hypertension). Short-acting nifedipine is not approved by U.S. Food and Drug Administration for management of hypertension.
Sodium nitroprusside	Use in rare cases of hypertension not responding to drugs listed here, for clinical findings of hypertensive encephalopathy or both. Start at a rate of 0.25 μg/kg/min to a maximum dose of 5 μg/kg/min). Fetal cyanide poisoning may occur if used for longer than 4 h.

BP, blood pressure.
[a]BP ≥160 mm Hg systolic, ≥105 mm Hg diastolic, or both, if sustained.
[b]For side effects, see *Physicians' Desk Reference*, 53rd ed. Montvale, NJ: Medical Economics Company Inc., 1999. Caution: Sudden and severe hypotension can result from administration of any of these agents, especially short-acting oral nifedipine. The goal of BP reduction in emergency situations should be a gradual reduction in BP to normal range. Clinical note: In managing hypertensive emergencies, the i.v. route is safer than oral or i.m. administration, because it is easier to combat inadvertent hypotension by stopping an i.v. injection or infusion than it is to stop intestinal or i.m. absorption of an orally or i.m. administered drug.
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TABLE 11-2. *Treatment of acute severe hypertension[a] in preeclampsia*

The most commonly used drug is hydralazine, administered either intravenously or intramuscularly, which, if given cautiously, is successful in most cases. It has been shown to be effective against preeclamptic hypertension (Paterson-Brown et al., 1994). Although this drug is sometimes given as an intravenous infusion, the pharmacokinetics (maximal effect at 20 minutes, duration of action 6 to 8 hours) indicate intermittent bolus injections are more sensible. A 5-mg bolus is given intravenously over 1 to 2 minutes. After 20 minutes, subsequent doses are dictated by the initial response. Once the desired effect is obtained, the drug is repeated as necessary (frequently in several hours). Parenteral labetalol has been shown to be effective for the treatment of acute severe hypertension in pregnancy (Magee et al., 1999). The drug may be used as intravenous bolus injections of 20 mg or 40 mg, or as continuous intravenous infusion of 1 mg per kg as needed. Labetalol is usually used as a second-line drug. It should be avoided in women with asthma and in those with congestive heart failure.

The use of oral nifedipine has been described in a limited number of women with acute severe hypertension during pregnancy (Vermil lion et al., 1999). Nifedipine acts rapidly, causing significant reduction in arterial blood pressure within 10 to 20 minutes of oral administration. Although it has favorable hemodynamic effects, physicians should be advised that rapidly acting nifedipine (in capsules containing the liquid form) has never been approved by the Food and Drug Administration for treating hypertension or hypertensive emergencies. . . . Care should be exercised when using nifedipine or any calcium antagonist with magnesium sulfate.

> In the rare case, sodium nitroprusside may be indicated after the failure of hydralazine, nifedipine, and labetalol for acute hypertensive emergency.

These recommendations are not universally endorsed. For instance, Magee et al. (1999) state that “for acute severe hypertension later in pregnancy, parenteral hydralazine is not the drug of choice as it is associated with more maternal and perinatal adverse effects than are other drugs, particularly intravenous labetalol or oral or sub-lingual nifedipine.” The National HBPEP Working Group may also be overly cautious about oral nifedipine. Vermillion et al. (1999) found it to control hypertension more rapidly than intravenous labetalol and to induce a significant increase in urinary output. In a review of all published data on nifedipine, Smith et al. (2000) conclude:

> Nifedipine is an effective drug to treat severe hypertension in pregnancy and preterm labour. Because it is given in a tablet or capsule by mouth, it is easier to use than intravenous drugs. The described side effects of nifedipine to the pregnant woman and her infant appear minimal. However, the studies of nifedipine are small and larger randomised trials are required before any recommendations can be made about the use of nifedipine in routine clinical practice.

Moreover, 94 children born to mothers who received nifedipine in pregnancy had no more problems at age 18 months than did children whose mothers took no antihypertensive drug (Bortolus et al., 2000). Calcium channel blockers are also used to prevent preterm labor and may be more effective and safer than magnesium sulfate (Larmon et al., 1999).

Even the one class of antihypertensive drugs that is contraindicated in pregnancy, the angiotensinconverting enzyme inhibitors, may be useful in women with severe, unresponsive vasoconstricted hypertension (Easterling et al., 2000). The successful use of low-dose captopril in these ten women was not associated with fetal or neonatal complications but, obviously, these drugs and angiotensin II–receptor blockers should not be used unless nothing else works.

Any drug used to lower BP during pregnancy may adversely affect fetal growth. In a metaanalysis of 45 trials involving 3,773 patients, mostly for hypertension of late onset in pregnancy, a fall of 10 mm Hg in mean BP was associated with a 145-g decrease in birth weight (von Dadelszen et al., 2000). This decrease was not related to the type or severity of hypertension nor to the type or length of therapy.

In an editorial about this report, de Swiet (2000) notes that, despite the need for caution in the use of antihypertensive drugs during pregnancy, the database is small and "to investigate the complex maternal and fetal variables relating to the outcome of pregnancy and anti-hypertensive therapy, much larger studies are necessary."

Until and if such studies are done, caution is obviously advised. Although diuretics are rarely advised, triamterene should be *specifically avoided* because it is a folic acid antagonist and may thereby increase the risk for birth defects (Hernández-Díaz et al., 2000). Perhaps the major point is that pregnant women should take as little medication as possible, a practice surely not practiced in France, where 99% of 1,000 pregnant women received a prescription for at least one drug, with a mean of 13.6 medications per woman, including many known to cause fetal risk (Lacroix et al., 2000).

Therapy for Severe Preeclampsia

Delivery may be indicated as soon as the mother is hemodynamically stable and glucocorticoids given to protect the fetus (Table 11-3). Intrauterine growth retardation is present in 30% of all preeclamptic pregnancies and is increasingly more severe the more severe the PE (Ødegård et al., 2000) so that it may be an indication for immediate delivery (Chammas et al., 2000).

Maternal	Fetal
Gestational age ≥38 wk*	Severe fetal growth restriction
Platelet count <100,000 cells/mm³	Nonreassuring fetal testing results
Progressive deterioration in hepatic function	Oligohydramnios
Progressive deterioration in renal function	
Suspected abruptio placentae	
Persistent severe headaches or visual changes	
Persistent severe epigastric pain, nausea, or vomiting	

*Delivery should be based on maternal and fetal conditions as well as on gestational age.
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TABLE 11-3. *Indications for delivery in preeclampsia*

Expectant management in a tertiary center is preferable both for the baby (Hall et al., 2000a) and the mother (Hall et al., 2000b). Whether such management should include prophylactic administration of magnesium sulfate to prevent eclampsia remains controversial (Duley and Neilson, 1999).

ECLAMPSIA

Eclampsia is defined by the occurrence of seizures due to hypertensive encephalopathy on the background of PE. This serious complication is becoming less common as better prenatal care is given. The present incidence in North America and Europe is estimated to be approximately 1 case in every 2,000 deliveries (Mattar and Sibai, 2000).

Clinical Features

Eclampsia is a form of hypertensive encephalopathy, with cerebral vasospasm and subsequent hyperperfusion accompanied by coagulopathy and fibrin deposition (Schwartz et al., 2000). The features were well defined among the 383 confirmed cases occurring throughout the United Kingdom during 1992 (Douglas and Redman, 1994): Eighty-five percent of the convulsions occurred within 1 week of the woman's last visit to a practitioner, 77% occurred in hospital, and 38% occurred before proteinuria and hypertension had been documented; 38% occurred antepartum; 18% of the women died and 35% had at least one major complication; the rate of stillbirths was 22/ 1,000; and the rate of neonatal deaths was 34/ 1,000.

In another group of 399 consecutive cases seen in Memphis, Tennessee, over an 11-year interval, these maternal complications were noted (Mattar and Sibai, 2000):

- Abruptio placentae (10%)
- The HELLP syndrome (11%)
- Disseminated intravascular coagulopathy (6%)
- Neurologic deficits and aspiration pneumonia (7%)
- Pulmonary edema (5%)
- Cardiopulmonary arrest (4%)
- Acute renal failure (4%)
- Death (1%)

Most of these were more common in those whose eclampsia appeared before 32 weeks' gestation, whereas neurologic deficits were more common with postpartum eclampsia. Cortical blindness occurs rarely (Apollon et al., 2000).

Management

Delivery is delayed until convulsions are stopped, the BP is controlled, and reasonable fluid and electrolyte balance has been established. With the following standardized treatment of 245 consecutive cases of eclampsia, only one maternal death occurred, and all but one of the fetuses survived who were alive when treatment was started and who weighed 1,800 g or more at birth (Pritchard et al., 1984):

- Magnesium sulfate to control convulsions
- Control of severe hypertension (diastolic BP, 110 mm Hg) with intermittent intravenous injections of hydralazine
- Avoidance of diuretics and hyperosmotic agents
- Limitation of fluid intake, unless fluid loss was excessive
- Delivery once convulsions are arrested and consciousness is regained

Long-Term Consequences

Considering the seriousness of eclampsia, many physicians have advised affected women that they should not become pregnant again. However, Chesley (1980) found that in 466 later pregnancies in 189 women who had had eclampsia, only 25% had recurrent hypertension and only 4 women had a second episode of eclampsia. In a 22- to 44-year follow-up of these women, the remote prognosis for those who had eclampsia during their first pregnancy was excellent (Chesley et al., 1976). The distribution of their BPs was identical to that of the general population.

The overall prognosis for all women who had hypertension during pregnancy was not as good, with more having subsequent hypertension (Nisell et al., 1995). However, other causes than PE were likely responsible for their hypertension during pregnancy and thereafter.

More women who survive preeclampsiaeclampsia later experience ischemic heart disease than do women with normotensive pregnancies (Seely, 1999). Therefore,

they need lifelong surveillance and measures to reduce cardiovascular risk.

CHRONIC HYPERTENSION AND PREGNANCY

Pregnant women may have any of the other types of hypertension listed in Table 1-6. Because the BP usually falls during the first half of pregnancy, preexisting hypertension may not be recognized if the woman is first seen during that time. If the pressure is high during the first 20 weeks, however, chronic hypertension rather than PE is almost always the cause.

Primary Hypertension Preceding Pregnancy

Pregnancy seems to bring out latent primary hypertension in certain women whose pressures return to normal between pregnancies but eventually remain elevated. In most patients, such “transient hypertension” appears late in gestation, is not accompanied by significant proteinuria or edema, and recedes within 10 days after delivery. Transient hypertension usually recurs during subsequent pregnancies and is often the basis for the misdiagnosis of PE in multiparous women (National HBPEP Working Group, 2000).

To elucidate the true nature of hypertension seen during a pregnancy, it is often necessary to follow up with the patient postpartum. By 3 months, complete resolution of the various changes seen in pregnancy will have resolved so that, if indicated, further studies to elucidate the cause of the hypertension can be obtained.

Risks to Mother and Fetus

Women with chronic hypertension have an increased risk for superimposed PE and placental abruption, and their babies have a three-fold greater risk for perinatal mortality (Ferrer et al., 2000). These risks are even greater for black women in the United States (Samadi et al., 1996), for those with a diastolic BP above 110 mm Hg during the first trimester, and for those with proteinuria early in pregnancy (Sibai et al., 1998). For those with serum creatinine exceeding 2.0 mg per dL, there is a one in three chance of entering end-stage renal failure after pregnancy (Epstein, 1996), so that these women should be strongly advised against pregnancy.

Moreover, even among women with mild, uncomplicated chronic hypertension who escape from superimposed PE, there is a greater risk for having small-for-gestational-age babies (Haelterman et al., 1997), thereby increasing the likelihood of subsequent hypertension in their children (see Chapter 3).

Management

Women with mild to moderate hypertension should be watched closely, warned about signs of early PE, and delivered at 37 weeks' gestation. They should be cautioned not to exercise intensively, told not to drink alcohol or smoke, and advised to restrict dietary sodium to 100 mmol per day (National HBPEP Working Group, 2000).

As to antihypertensive drug therapy for women with stage 1 or 2 hypertension (i.e., BP, 140–180/90–110 mm Hg), there is no evidence that such therapy improves neonatal outcomes (Ferrer et al., 2000). As stated in the report of the National HBPEP Study Group (2000):

> The value of continued administration of anti-hypertensive drugs to pregnant women with chronic hypertension continues to be an area of debate. Although it may be beneficial for the mother with hypertension to reduce her blood pressure, lower pressure may impair uteroplacental perfusion and thereby jeopardize fetal development.
>
> . . . On the basis of the available data, some centers currently manage women with chronic hypertension by stopping antihypertensive medications under close observation. In patients with hypertension for several years, with evidence of target organ damage, or on multiple antihypertensive agents, medications may be tapered on the basis of blood pressure readings but should be continued if needed to control blood pressure. End points for reinstituting treatment include exceeding threshold blood pressure levels of 150 to 160 mm Hg systolic or 100 to 110 mm Hg diastolic or the presence of target organ damage such as left ventricular hypertrophy or renal insufficiency.
>
> Methyldopa is preferred by most practitioners. Alternatively, women who are well controlled on antihypertensive therapy before pregnancy may be kept on the same agents (with the exception of angiotensin-converting enzyme inhibitors, [and] AII [angiotensin II] receptor antagonists) during pregnancy. . . . If methyldopa is ineffective, alternatives can be substituted based on rational considerations of mechanisms of action. In the latter respect, salt retention may cause refractoriness to vasodilator therapy, in which case a diuretic added to the regimen restores blood pressure control and permits prolongation of the pregnancy.
>
> Most of the published experience with other agents comes from trials using adrenergicblocking drugs including beta-blockers and the alpha-beta-blocker labetalol. There is a suggestion that beta-blockers prescribed early in pregnancy, specifically atenolol, may be associated with growth restriction. On the other hand, none of these agents have been associated with any consistent ill effects; however, long-term followup studies are lacking.
>
> Experience with calcium antagonists is limited, with most reported uses being late in pregnancy. . . . The use of diuretic agents in pregnancy is controversial. . . . However, if their use is indicated, they are safe and efficacious agents, can markedly potentiate the response to other antihypertensive agents, and are not contraindicated in pregnancy except in settings where uteroplacental perfusion is already reduced (preeclampsia and intrauterine growth restriction). Although data concerning the use of diuretics in pregnant women with essential hypertension are sparse, this working group concluded that gestation does not preclude use of diuretic drugs to reduce or control blood pressure in women whose hypertension predated conception or manifested before midpregnancy.
>
> Angiotensin-converting enzyme inhibitors are contraindicated during pregnancy because of associations with fetal growth restriction, oligohydramnios, neonatal renal failure, and neonatal death. Although no data are available on human use of angiotensin II receptor antagonists, adverse effects are likely to be similar to those reported with angiotensin-converting enzyme inhibitors, and these agents should be avoided.

Presence of Renal Disease

Women with even mild renal insufficiency have a higher incidence of superimposed PE and a tenfold higher risk of fetal loss (Junkers et al., 1997). Those with more severe renal insufficiency (i.e., serum creatinine >1.5 mg per dL) have even more difficulty. Nonetheless, successful pregnancies have been reported in most women who conceive during chronic dialysis (Bagon et al., 1998) or after renal transplantation (Hou, 1999).

Presence of Diabetes

A dramatic reduction in perinatal mortality in diabetic pregnancy has occurred over the last 30 years by strict glycemic control before and during gestation, intensive obstetric monitoring, and neonatal care (Pearson and Copland, 1999). These women should always be managed by obstetricians experienced in this area.

Other Causes of Hypertension during Pregnancy

Secondary forms of hypertension (described in other chapters) occur only rarely during pregnancy (Keely, 1998). Their diagnosis may be confounded by the multiple changes in the renin-aldosterone and other hormonal systems that occur during pregnancy and their therapy may be made difficult by adverse effects on the fetus. Coverage of these various identifiable forms of hypertension during pregnancy is provided in the respective chapters.

POSTPARTUM SYNDROMES

In women who were preeclamptic, continued close monitoring is needed after delivery (Walker, 2000). If prophylactic anticonvulsants were given before delivery, they should be continued for 24 hours. Depending on the BP, the doses of antihypertensive drugs should be reduced and they may not be needed for some weeks. If BP remains elevated at 6 weeks postpartum, further investigation for other causes of hypertension should be provided.

As noted earlier, PE and eclampsia may appear after delivery.

Peripartum cardiomyopathy is a rare but serious form of left ventricular systolic dysfunction that appears in the last month of pregnancy or within 5 months after delivery in the absence of identifiable causes or prior recognizable heart disease (Pearson et al., 2000). Endomyocardial biopsy often reveals myocarditis (Felker et al., 2000).

Fulminant nephrosclerosis may appear postpartum and rapidly proceed into oliguric renal failure with severe hypertension (Ferris, 1995).

Hypertension and Lactation

Breast-feeding does not raise the mother's BP (Robson et al., 1989), but bromocriptine mesylate used for suppression of lactation may induce hypertension (Chan et al., 1994). All antihypertensive drugs taken by mothers enter their breast milk; most are present in very low concentrations, except most b-blockers other than propranolol (Ito, 2000).

As noted by the National HBPEP Working Group (2000) :

> No data on calcium-channel blockers and lactation have been reported. Diuretics may reduce milk volume and suppress lactation. Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists should be avoided on the basis of reports of adverse fetal and neonatal renal effects. Given the scarcity of data, breastfed infants of mothers taking antihypertensive agents should be closely monitored for potential adverse effects.

Postpartum Follow-Up

Women who were hypertensive during pregnancy need counseling about the risks of future pregnancies and future cardiovascular events. These are the recommendations of the National HBPEP Working Group (2000) :

> If preeclampsia occurred late in an initial gestation, there is no evidence of remote cardiovascular risk, but subsequent pregnancies will help us define risk more accurately. Women with early onset disease, multiparous women with preeclampsia or only hypertension, and those manifesting gestational hypertension in any pregnancy are at increased cardiovascular risk—information of importance for long-term health care strategies. The best news, however, is that women experiencing normotensive birth have a reduced risk for remote hypertension.

HYPERTENSION WITH ORAL CONTRACEPTIVES

OCs have been used by millions of women since the early 1960s. OCs are safe for most women, but their use carries some risk.

Incidence of Hypertension

The BP rises a little in most women who take estrogen-containing OCs (Heintz et al., 1996) (Fig. 11-6). In a prospective cohort study of almost 70,000 nurses covering the 4 years between 1989 and 1993, the overall relative risk for hypertension was 50% higher for current OC users as compared to never-users and 10% higher as compared to former users (Chasan-Taber et al., 1996). The 50% increase in relative risk translated to 41 cases per 10,000 person-years of OC use.

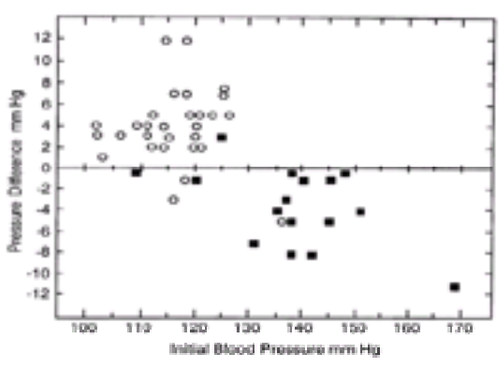

FIG. 11-6. Effects of oral contraceptives (*circles*) and postmenopausal estrogen replacement therapy (*squares*) on systolic blood pressure as noted in longitudinal and cross-sectional studies reported up to 1985. [Reprinted from McCaffrey TA. *Estrogens and blood pressure: a theoretical review* (dissertation). Lafayette, IN: Purdue University, June 1985, with permission.]

The first report of OC-induced hypertension appeared a few years after their introduction (Brownrigg, 1962); the association was clearly defined in 1967 (Laragh et al., 1967; Woods, 1967). Not until a prospective study was begun in Glasgow did it become apparent that the BP rose in most women who started OCs. Among 186 women who took estrogen-containing OCs for 2 years, systolic BP rose in 164 and diastolic BP in 150 (Weir, 1982). The incidence of hypertension may be less with present-day, lower-dose formulations containing as little as 15 mg estrogen and new synthetic progestogens (Kubba et al., 2000).

Predisposing Factors

In the prospective U.S. Nurses Study, the risk for hypertension was not significantly modified by age, family history of hypertension, ethnicity, or body mass index (Chasan-Taber et al., 1996). Women with prior PE seem to carry little additional risk: Only 9 of 180 women who had PE had a rise in diastolic BP beyond 90 mm Hg after 6 months to 2 years of OC use (Pritchard and Pritchard, 1977). Women with preexisting primary hypertension may be more susceptible (Narkiewicz et al., 1995).

Clinical Course

In most women who develop hypertension while taking an OC, the disease is mild and, in more than half, the BP returns to normal when the OC is stopped (Weir, 1978). In a few women, the hypertension is severe, rapidly accelerating into a malignant phase and causing irreversible renal damage (Lim et al., 1987). A hemolytic uremic syndrome may also follow OC use (Hauglustaine et al., 1981). Even in patients with reversible hypertension, considerable renal damage may sometimes be found by means of arteriography and renal biopsy (Boyd et al., 1975), and proteinuria may persist (Rib-stein et al., 1999).

Among nulliparous women who had recently stopped OCs and became pregnant, the risk for developing GH was reduced but the risk for PE slightly increased (Thadhani et al., 1999).

Mechanism

Whether OCs cause hypertension *de novo* or simply uncover the propensity toward primary hypertension that would eventually appear spontaneously is unknown. The mechanism for OC-induced hypertension is also unknown, particularly because estrogen appears to be vasodilative (Lee et al., 2000). Changes in hemodynamics, renin-angiotensin-aldosterone, insulin sensitivity, and erythrocyte cation transport have been identified. As noted, both the estrogen and the progestogen may be responsible.

Hemodynamic Changes

With the then-used high-dose OCs, Walters and Lim (1970) and Lehtovirta (1974) found that body weight, plasma volume, and cardiac output were significantly increased in previously normal women after 2 to 3 months of OC use. Crane and Harris (1978) found a 100- to 200-mEq increase in total body exchangeable sodium after 3 weeks' intake of stilbestrol, conjugated estrogens, estradiol, or mestranol. They also found that some of the progestogens used in the OCs, including norethindrone, caused comparable sodium retention when given to normal subjects.

Renin-Angiotensin-Aldosterone Changes

Estrogens increase the hepatic synthesis of renin substrate (Helmer and Judson, 1967) by inducing the expression of angiotensinogen mRNA (Gordon et al., 1992). The increase in substrate is accompanied by an increase in total renin activity but a fall in the concentration of renin (Derkx et al., 1986). These changes in

renin-angiotensin-aldosterone likely do not contribute to the hypertension, as angiotensin-converting enzyme inhibitors had no greater effect in OC-induced hypertension than in essential hypertension (Ribstein et al., 1999).

In most women on OCs, the renal vasculature responds to the higher levels of angiotensin II with a reduction in renal blood flow (Hollenberg et al., 1976). Although the mean fall was 25% in this study, in some women it was as high as 50%. Perhaps women with the greatest renal vasoconstriction develop sodium retention and hypertension.

Insulin Resistance

In view of the potential role of insulin resistance in the pathogenesis of primary hypertension, as described in Chapter 3, it is noteworthy that OCs with 30 to 40 mg of ethinyl estradiol induce insulin resistance, whereas progestin-only pills prolong the half-life of insulin (Godsland et al., 1992).

Risks in Perspective

With previous, high-dose formulations, the risks for various cardiovascular diseases, including hypertension, were increased. With currently used low-dose formulations, there are *no* increased risks for overall mortality or myocardial infarction, a reduced risk for ovarian cancer, but an increased risk for venous thromboembolism, stroke, and cervical and breast cancer (Beral et al., 1999). The increase in stroke risk translates to one additional ischemic stroke per year per 24,000 nonsmoking, normotensive women using low-estrogen OCs (Gillum et al., 2000). The increase in breast cancer translates to one extra case in every 1,000 users by age 45 who stopped OCs at age 34, in addition to ten cases due to background risk (Kubba et al., 2000).

To put the dangers of OC in proper perspective, its use in women aged 15 to 34 who do not smoke is associated with *less risk of death* than are most other contraceptive methods, particularly when its lower rate of failure to prevent pregnancy is considered (Ory, 1983). Only the condom, plus abortion if the condom fails, is safer and more effective than OCs.

Guidelines for Use of Oral Contraceptives

OCs should not be given to smokers older than 35 years or to women with systemic lupus erythematosus or prior thromboembolic disease. They should be given cautiously to women with migraine headaches but may be used in those with diabetes, obesity, sickle-cell disease, and most other coexisting problems (Speroff, 1996). When OCs are used, the following precautions should be taken:

- The lowest effective dose of estrogen and progestogen should be dispensed.
- The BP should be taken at least every 6 months and whenever the woman feels ill.
- If the BP rises significantly, the pill should be stopped and another form of contraceptive should be provided.
- If the BP does not become normal within 3 months, appropriate workup and therapy should be provided.
- If no alternative form of contraception is feasible and OCs must be continued, antihypertensive therapy may be needed to control the BP.

HYPERTENSION AND ESTROGEN REPLACEMENT THERAPY

An even larger number of women will likely begin postmenopausal estrogen replacement therapy (ERT) than will use estrogen-containing OCs. There have been conflicting data about protective effects of ERT on cardiovascular risk, but most recent studies have found an increase in risk during the first year of ERT and a decreased risk with continued therapy (Grady and Hulley, 2001; Heckbert et al., 2001; Viscoli et al., 2001). Some of the reported benefits of ERT may have been exaggerated because women who use ERT are healthier than nonusers (Rödström et al., 1999). Nonetheless, the multiple improvements in various menopausal symptoms, cardiovascular risk factors, and bone structure seen with ERT (Tolbert and Oparil, 2001) will support its use in many women while the results of additional controlled trials are awaited. If the lower prevalence of Alzheimer's disease (Baldereschi et al., 1998) and slower loss of cognitive function (Yaffe et al., 2000) reported in women given ERT are confirmed, even greater use will follow.

In view of the known prohypertensive effect of estrogens given in superphysiologic doses for contraception, there are concerns that the smaller doses for replacement might also raise the BP, adding to the frequent rise in BP after menopause related to increased body weight and aging (Wassertheil-Smoller et al., 2000). Although hypertension has been reported with postmenopausal estrogen use (Crane et al., 1971), most controlled trials find a *decrease* in ambulatory BP and a greater dipping of nocturnal BP in ERT users (Angerer et al., 2000; Butkevich et al., 2000; Cagnacci et al., 1999); Seely et al., 1999; Van Ittersum et al., 1998). Most women who are already hypertensive have a fall in BP with transdermal estradiol (Mercuro et al., 1998; Modena et al., 1999). ERT was found to reduce proteinuria and increase creatinine clearance in 16 diabetic, hypertensive, postmenopausal women (Szekacs et al., 2000) and to be associated with decreased intimamedia thickness of the common carotid artery and risk of peripheral vascular disease in elderly women (Westendorp et al., 1999 , 2000).

The differences between OCs and ERT, as noted by McCaffrey (1985), are striking (Fig. 11-6). The often lower pressures with ERT may reflect a number of antihypertensive effects of estrogen replacement, including the following:

- Improved endothelium-dependent vasodilation (Higashi et al., 2001) that reflects increased endothelium-mediated nitric oxide activity (Majmudar et al., 2000), increased circulating bradykinin (Sumino et al., 1999), and decreased pressor response to norepinephrine (Sung et al., 1999). The improvements in endothelial function were not associated with changes in large artery stiffness or insulin sensitivity (Vehkavaara et al., 2000).
- Improved baroreceptor sensitivity (De Meersman et al., 1998).
- Reduced muscle sympathetic nerve activity (Vongpatanasin et al., 2001).
- Inhibition of vascular smooth muscle cell– dependent adventitial fibroblast migration (Li et al., 1999).

Thus, although the clinical evidence favoring ERT after menopause for protection against cardiovascular diseases remains in doubt, hypertension is not usually a concern and may, in fact, be ameliorated.

We will turn next to less common causes of secondary hypertension involving the adrenal glands; although relatively rare, they often must be excluded.

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12
Pheochromocytoma (with a Preface about Incidental Adrenal Masses)

INCIDENTAL ADRENAL MASS

Before considering adrenal causes of hypertension in this and the subsequent two chapters, the management of incidentally discovered adrenal masses will be covered. Such masses are being found increasingly during abdominal computed tomography (CT) and magnetic resonance imaging (MRI) in patients undergoing imaging for an unrelated reason and who have no clinical evidence of adrenal hyperfunction. They must be evaluated, both because they may be functionally active and because they may be malignant (Young, 2000). If the evaluation is negative, the patient should be reassured about the low likelihood of future trouble; a repeat imaging procedure and screening for adrenal hyperfunction should be done after 1 year, but repeated evaluations are rarely indicated in the continued absence of clinical abnormalities. Logically, only those masses that are neither malignant nor hyperfunctioning should be called *incidentalomas*.

Incidence

Adrenal masses were found in 5.9% of 87,065 autopsies in 25 studies (Young, 2000). The prevalence increases progressively with age. However, the prevalence of incidental adrenal masses on CT imaging in most surveys published in the 1980s and early 1990s has aver-aged only 0.9%. As scanners with improved resolution are being used for more and more indications, the recognition of incidental adrenal masses will likely continue to increase.

Evaluation

In patients without known primary cancers, the majority of incidental adrenal masses are benign; in patients without clinical evidence of adrenal hyperfunction, the majority are nonfunctional. Nonetheless, every adrenal mass should be evaluated to rule out malignancy and hypersecretion. Therefore, the evaluation should use procedures that are readily available and relatively inexpensive.

Workup for Malignancy

Imaging

Masses that are small, smooth, and have a high fat content are usually benign adenomas or, less commonly, myelolipomas (Udelsman and Fishman, 2000). These high-fat lesions have a low density on CT and are isointense to liver on T_2-weighted MRI. Chemical shift MRI can also demonstrate lipid within the adrenal mass. Even better discrimination has been found with the relative percentage enhancement washout of contrast-enhanced CT: Almost all benign lesions have greater than 50% washout, and metastases less than 50% (Peña et al., 2000).

Size alone is no longer considered to be the primary indicator of malignancy, as some cancers are smaller than 3 cm and some benign nonfunctioning adenomas are as large as 15 cm (Copeland, 1999). However, Copeland recommends that masses larger than 4 cm in diameter be resected if there is any question of whether it is benign by imaging characteristics.

Adrenal Scintigraphy

Adrenal scintigraphy with an iodinated cholesterol derivative (NP-59) that localizes in functioning adrenocortical tissue but not in most malignant adrenal masses has been used by Gross et al. (1994) in 229 euadrenal patients with unilateral masses found on CT scans. Adrenal masses that took up the NP-59 were almost always benign; those that did not take up the NP-59 were mostly malignant, either metastatic or primary. Although scintigraphy may provide more certainty, most radiologists depend on CT or MRI criteria alone.

Biopsy

Fine-needle aspiration biopsy is rarely needed, because imaging characteristics can usually be relied on to exclude malignancy (Young, 2000).

Hormonal Levels

In one series of 129 adrenal cancers, 40 had manifestations of endocrinopathy, most commonly of excess cortisol or androgen (Crucitti et al., 1996). High levels of plasma dehydroepiandrosterone sulfate are seen in some adrenocortical cancers, whereas low levels are seen in nearly two-thirds of benign adenomas (Terzolo et al., 1996).

Workup for Hyperfunction

Table 12-1 lists the suggestive clinical features and scanning tests for adrenal hyper-function. In 13 published series reporting a total of 2,005 patients, the percentages of patients with hormonal hypersecretions were 5.3% with preclinical Cushing's syndrome, 5.1% with pheochromocytoma (pheo), and 1.0% with primary aldosteronism (Young, 2000).

Diagnosis	Suggestive clinical features	Laboratory screening tests
Pheochromocytoma	Paroxysmal hypertension; spells of sweating, headache, palpitations	Plasma or spot-urine metanephrine
Cushing's syndrome	Truncal obesity; thin skin; muscle weakness	8 a.m. plasma cortisol after 1 mg dexamethasone at bedtime
Primary aldosteronism	Hypertension; weakness	Serum potassium; if low, urinary potassium excretion; plasma aldosterone and renin
Adrenocortical carcinoma	Virilization or feminization	Plasma dehydroepiandrosterone, testosterone, or estrogens

TABLE 12-1. *Evaluation of incidental adrenal masses*

Whereas subclinical pheos and aldosteronomas should usually be resected, uncertainty remains about the management of subclinical Cushing's syndrome. The presence of diabetes, hypertension (Rossi et al., 2000), and reduced bone density (Torlontano et al., 1999) may be indications for surgery. The wisdom of simply observing the majority is supported by the absence of malignancy over an average follow-up of 50 months in 238 patients with tumors that averaged 2.5 cm in size (Young, 2000). Enlargement or hyperfunction may occur so that continued observation is needed (Barzon and Boscaro, 2000) but, if no growth or hyper-function is noted after 1 year, only routine follow-up is needed.

OVERVIEW OF ADRENAL HYPERFUNCTION

Beyond the need to evaluate patients with incidentally discovered adrenal masses, an adrenal cause for hypertension will need to be considered much more frequently than the low prevalence—likely less than 1.0%—of these causes would suggest. The presence of adrenal hyper-function is often considered in the evaluation of hypertensive patients, because many of the symptoms and signs of adrenal hyperfunction are nonspecific and are encountered in patients with normal adrenal function. Recurrent spells suggestive of pheo, hypokalemia pointing to primary aldosteronism, and cushingoid features are all encountered in many more patients than the relatively few who turn out to have these diseases. Of all of these, consideration of a pheo is likely most important.

PHEOCHROMOCYTOMA

The presence of a pheo should be considered in all hypertensives because, if not recognized, a pheo may provoke fatal hypertensive crises during anesthesia and other stresses (Prys-Roberts, 2000). Pheos are often unrecognized: At the Mayo Clinic from 1928 to 1977, of 54 pheos found at autopsy, only 13 had been diagnosed during life (Lie et al., 1980). Of the 41 previously unrecognized, death was related to the manifestations of the tumor in 30 patients. This experience with unrecognized pheos should be contrasted to the excellent results obtained at the Mayo Clinic in 138 patients with demonstrated pheos who underwent surgery during these years; the survival curve of those with a benign pheo was similar to that of the normal population (Sheps et al., 1990). In subsequent years, no perioperative mortality occurred in 143 patients, in all but three of whom the diagnosis was made preoperatively (Kinney et al., 2000).

Incidence

Pheos are rare: One per 2,031 autopsies was found (McNeil et al., 2000). The incidence of pheos diagnosed during life or at autopsy among the residents of Rochester, Minnesota—the location of the Mayo Clinic—was found to be 0.95 cases per 100,000 person-years (Beard et al., 1983). This figure, the most accurate estimate of the incidence of the tumor now available, suggests that if 20% of the adult population is hypertensive, only approximately five pheos would be expected to be found among 100,000 hypertensives each year.

Pathophysiology

Development

The cells of the sympathetic nervous system arise from the primitive neural crest as primordial stem cells, called *sympathogonia* (Fig. 12-1). The sympathogonia migrate out of the central nervous system to occupy a place behind the aorta. These stem cells may differentiate into either sympathoblasts, which give rise to sympathetic ganglion cells, or pheochromoblasts, which give rise to chromaffin cells. As seen in Figure 12-1, tumors may arise from each of these cell lines, often sharing histologic and biochemical characteristics. These include highly malignant neuroblastomas, arising from sympathoblasts, and ganglioneuromas, which are usually more benign. These tumors are rarely seen after adolescence and are usually recognized by the excretion of large amounts of homovanillic acid, the urinary metabolite of dopamine (Fig. 12-2).

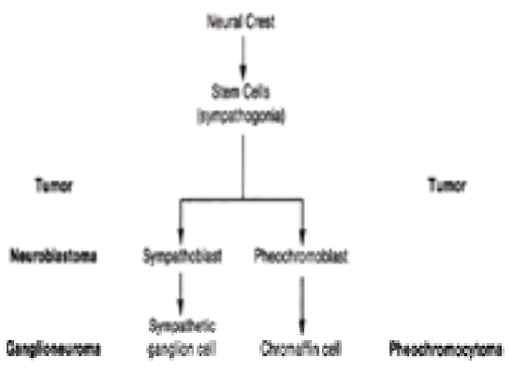

FIG. 12-1. Developmental pathway for sympathetic ganglion and chromaffin cells and the tumors that may arise from them.

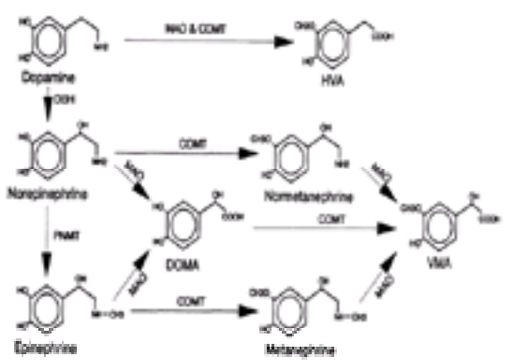

FIG. 12-2. Pathways and enzymes of catecholamine metabolism. The excretory products are shown on the right of the biosynthetic pathway. COMT, catechol O-methyltransferase; DBH, dopamine b-hydroxylase; DOMA, dihydroxyphenylglycol; HVA, homovanillic acid; MAO, monoamine oxidase; PNMT, phenylethylamine N-methyltransferase; VMA, vanillylmandelic acid.

The chromaffin cells, which have the capacity to synthesize and store catecholamines, therefore staining brown on treatment with chromium, are found mainly in the adrenal medulla. They also appear in the sympathetic ganglia and paraganglia that lie along the sympathetic chain and organ of Zuckerkandl, located anteriorly at the bifurcation of the aorta. In a developmental sense, the adrenal medulla may be considered a sympathetic ganglion that lacks postsynaptic fibers. In a functional sense, its chromaffin cells differ from the rest by having the capacity to convert norepinephrine (NE) to epinephrine (Epi) (Fig. 12-2).

Location and Tumor Nomenclature

Table 12-2 shows where chromaffin cell tumors (i.e., pheos) have been found. As many as 15% of pheos in adults and 30% in children are extraadrenal; they may be located anywhere along the sympathetic chain and, rarely, in aberrant sites (Whalen et al., 1992). Those functioning tumors arising outside the adrenal medulla are best termed *extraadrenal pheos* (Whalen et al., 1992), whereas nonsecreting extraadrenal tumors are termed *paragangliomas* (Fonseca and Bouloux, 1993). Paragangliomas that arise from the specialized chemoreceptor tissue in the carotid body, glomus jugulare, and aortic body have been separately classified as *chemodectomas*, and they may secrete catecholamines (Erickson et al., 2001).

Location	Percent
Intraabdominal	97–99
Single adrenal tumor	50–70
Single extraadrenal tumor[a]	10–20
Multiple tumors[b]	15–40
Bilateral adrenal tumors	5–25
Multiple extraadrenal tumors	5–15
Outside the abdomen	1–3
Intrathoracic[c]	2
In the neck	<1

[a]Along the sympathetic chain: lumbar, paravertebral, epigastrium, bladder.
[b]More common in children and in familial syndrome with medullary thyroid cancer.
[c]Usually in the posterior mediastinum.

TABLE 12-2. *Location of pheochromocytoma*

In their review, Whalen et al. (1992) noted that at least 85% of extraadrenal pheos have been below the diaphragm, nearly half in the superior paraaortic areas. The inferior paraaortic area, below the kidneys to the aortic bifurcation, is the next most common site, with most of these lesions being in the organs of Zuckerkandl. Approximately 10% are in the bladder (Crecelius and Bellah, 1995), and another 10% are in the thorax, including almost 40 cases in the heart (Lin et al., 1999). A few rise in the head and neck or in the pelvis. Extraadrenal pheos may more likely be malignant as compared to adrenal pheos (Goldstein et al., 1999). A larger proportion of extraadrenal and multicentric pheos are found in children than in adults.

On the other hand, the majority of the 297 benign paragangliomas seen over a 20-year interval at the Mayo Clinic were located in the head and neck (Erickson et al., 2001). Of the 49 of these tumors that were hyperfunctioning (i.e., extraadrenal pheos), 36 were below the diaphragm, but 9 were in the head and neck and 4 in the thorax.

Chromaffin Cell Secretion

The chromaffin cells synthesize catecholamines from the dietary amino acid tyrosine, which is converted into dopa and then dopamine. As seen in Figure 12-2, NE is the end product, except in the adrenal medulla, where more than 75% of the NE is methylated into Epi. Most adrenal medullary pheos secrete some Epi, but a few, usually small in size and having a rapid turnover of catecholamines, secrete only NE (Crout and Sjöerdsma, 1964). On the other hand, extraadrenal pheos only rarely secrete Epi (Blumenfeld et al., 1993).

When catecholamines are released by exocytosis from adrenal storage vesicles, there is a coupled, proportional release of the enzyme dopamine b-hydroxylase and the soluble proteins chromogranin A, B, and C. Plasma chromogranin A and B levels are elevated in patients with pheos and other neuroendocrine tumors and may serve as sensitive markers (Granberg et al., 1999). Plasma chromogranin A levels are usually markedly elevated with malignant pheos and may be used to monitor the response to therapy (Rao et al., 2000).

Patterns of Catechol Secretion

Secretion from pheos varies considerably. Small pheos tend to secrete larger proportions of active catecholamines; larger pheos, with the capacity to store and metabolize large quantities of catecholamines, tend to secrete less of their content, and most of that may be secreted in inactive forms.

The frequency and severity of symptoms and signs likely relate to the secretory pattern of the pheo. Those that continuously release large amounts of catecholamines may induce sustained hypertension with few paroxysms, as the adrenergic receptors become desensitized after prolonged exposure to their agonists (Valet et al., 1988); those that are less active but cyclically release their catecholamine stores may induce striking paroxysms of hypertension with the classic symptoms of a pheo, because the receptors are more responsive.

The nature of the signs and symptoms also reflects the predominant catecholamine that is secreted. NE produces more a-mediated vasoconstriction with diastolic hypertension; and Epi produces more b-mediated cardiac stimulation with predominantly systolic hypertension, tachycardia, sweating, flushing, and tremulousness (Ito et al., 1992).

Dopa and Dopamine

Pheos that secrete large amounts of the vasodilating precursors dopa and dopamine may not manifest hypertension. This could explain the rarity of symptoms in patients with neuroblastomas and in some patients with malignant pheos who hypersecrete dopa and dopamine (Goldstein et al., 1986). Kuchel (1998) has found isolated increased plasma dopamine in patients with pheolike symptoms.

Other Secretions

Table 12-3 lists various peptide hormones that may be released concomitantly with catecholamines from pheos; their secretion may be associated with various clinical manifestations (Fonseca and Bouloux, 1993).

Peptide	Manifestation
Adrenomedullin	Vasodilatation
Angiotensin-converting enzyme	Hypertension
Atrial natriuretic factor	Polyuria, hypotension(?)
Calcitonin	—
Calcitonin gene-related peptide	Vasodilatation
Chromogranin A	—
Corticotrophin-releasing factor, adrenocorticotrophin	Hypercorticotism
Endothelin	Vasoconstriction
Enkephalins	Constipation
Erythropoietin-like factor	Polycythemia
Human growth hormone–releasing hormone	Acromegaly
Insulinlike growth factor II	Related to tumor growth(?)
Interleukin-6	Pyrexia
Motilin	Diarrhea
Neurone-specific enolase	—
Neuropeptide Y	Vasoconstriction
Parathormone	Hypercalcaemia
Parathormone-related peptide	Hypercalcaemia
Pituitary adenylate cyclase activating polypeptide	Vasodilatation, interleukin-6 release
Renin	Vasoconstriction
Somatostatin	Constipation
Substance P	Flushing
Vasoactive intestinal peptide	Flushing, diarrhea

Modified from Fonseca V, Bouloux P-MG. Pheochromocytoma and paraganglioma. Baillieres Clin Endocrinol Metab 1993;7:509–545.

TABLE 12-3. *Secretory peptides from pheochromocytomas and their manifestation*

Hemodynamics

The hemodynamics in 24 patients with a pheo were little different from those in age-, gender-, and weight-matched patients with essential hypertension, despite the tenfold higher plasma NE levels in the pheo patients (Bravo, 1994). The major finding in both was an increased peripheral resistance, whereas the pheo patients had lower blood volumes. Heart rate is usually approximately 90 beats per minute, even when the blood pressure (BP) is not high, but cardiac output is usually normal, except during surges of Epi release.

Patients with symptoms that may suggest a pheo but that are caused by a hyper-b-adrenergic state have a high cardiac output, whereas those with idiopathic hypovolemia are normotensive (Fouad-Tarazi et al., 1995).

With ambulatory BP monitoring, pheo patients may not have a nocturnal fall in BP and show a negative relation between pulse and BP (Meisel et al., 1994).

Clinical Features

Table 12-4 summarizes the varied and often dramatic symptoms and signs of catecholamine excess. Most patients have headache, sweating, and palpitations; and many have all three occurring in paroxysms. Although most patients have lost some weight, 8 of 22 patients in one series were 10% or more overweight, and 4 were definitely obese (Lee and Rousseau, 1967). By definition, the 5% of incidental adrenal masses that turn out to be pheos are asymptomatic (Young, 2000).

Common (>33% of patients)
Hypertension (probably >90%)
Intermittent only (2–50%)
Sustained (50–60%)
Paroxysms superimposed (~50%)
Hypotension, orthostatic (10–50%)
Headache (40–60%)
Sweating (40–70%)
Palpitations and tachycardia (45–70%)
Pallor (40–45%)
Anxiety and nervousness (20–40%)
Nausea and vomiting (20–40%)
Fundoscopic changes (50–70%)
Weight loss (60–80%)
Less common (<33% of patients)
Tremor
Abdominal pain
Chest pain
Polydipsia, polyuria
Acrocyanosis, cold extremities
Flushing
Dyspnea
Dizziness, syncope
Convulsions
Bradycardia
Fever
Thyroid swelling
Data from 370 reported cases, analyzed by Ross and Griffith (1989) and Wenbel and Ober (1995).

TABLE 12-4. *Symptoms and signs of pheochromocytoma*

Symptoms

Paroxysmal Hypertension

The paroxysms represent the classic picture of the disease, but only paroxysmal hypertension with intervening normotension is relatively uncommon. Most patients have sustained hypertension with superimposed paroxysms. The paroxysm can be brought on in multiple ways, including exercise, bending over, urination, defecation, an enema, induction of anesthesia, smoking, dipping snuff, palpation of the abdomen, or pressure from an enlarging uterus during pregnancy. Episodes may follow the use of multiple drugs, acting in various ways:

- Increase catecholamine synthesis (e.g., adrenocorticotropic hormone) (Jan et al., 1990)
- Increase catecholamine release (e.g., histamine, opiates, or nicotine) (McPhaul et al., 1984)
- Antagonize dopamine (e.g., droperidol) (Montiel et al., 1986)
- Inhibit catechol reuptake (e.g., tricyclic antidepressants) (Achong and Keane, 1981)
- Inhibit serotonin reuptake (Seelen et al., 1997)

Wide episodic fluctuations of BP may occur spontaneously and may be related to an impaired baroreceptor reflex (Muneta et al., 1992) or withdrawal of vagal tone (Dabrowska et al., 1995).

The episodes vary in frequency, duration, and severity. They may occur many times per day or only every few months, but most patients experience at least one episode per week. Patients are often considered psychoneurotic, particularly if they describe a sensation of tightness starting in the abdomen and rising into the chest and head, anxiety, tremors, sweating, and palpitations, followed by marked weakness. On the other hand, pheolike symptoms and paroxysms of marked hypertension may be seen with emotional reactions and panic attacks (Mann, 1999).

Pheo episodes, sometimes with BP exceeding 250/150 mm Hg, may lead to myocardial ischemia (DeBacker et al., 2000), cardiomyopathy with acute congestive heart failure (Sardesai et al., 1990), or arrhythmias (Shimizu et al., 1992). Rarely, the presentation may be as an acute abdomen from spontaneous rupture of the tumor (Tanaka et al., 1994), sudden death after minor abdominal trauma (Primhak et al., 1986), lactic acidosis (Bornemann et al., 1986), or high fever and encephalopathy (Newell et al., 1988). Tumors arising in the wall of the bladder may cause symptoms only with micturition and, in approximately half of such cases, produce painless hematuria (Thrasher et al., 1993).

In patients with predominant Epi secretion, b-blockers can raise the BP by blocking the b_2-mediated vasodilator action of Epi, leaving the a-mediated vasoconstrictor action unopposed. Those with NE-producing pheos likely will not have a pressor response to b-blockers, because NE has little action on vasodilative b_2-receptors (Plouin et al., 1979).

Hypotension

Patients with a pheo secreting predominantly Epi may, although rarely, have profound hypotension with sweating, fever, and ventricular arrhythmias. Prolonged hypotension may also occur by spontaneous necrosis of the tumor (Atuk et al., 1977) or after administration of a phenothiazine (Lund-Johansen, 1962) or an a-blocker (Watson et al., 1990). Much more commonly, patients have modest falls in BP on standing, associated with tachycardia and dizziness. Such orthostatic changes in the face of exaggerated rises in circulating catechols reflect reduced responsiveness of the arteries and veins to NE, probably from down-regulation of a-receptors after prolonged exposure to high levels of the agonist (Streeten and Anderson, 1996) and from suppressed central sympathetic outflow (Grassi et al., 1999). Postural hypotension in an untreated, nonelderly hypertensive may be a clue to the presence of a pheo.

Other Associated Diseases

Other diseases associated with a pheo include the following:

- *Cholelithiasis*, seen in up to 30% of patients (Gifford et al., 1994).
- *Diabetes*, with fasting glucose levels higher than 125 mg per dL in 14 of 60 patients (Stenström et al., 1984).
- *Hypercalcemia* in the absence of hyperparathyroidism (Kimura et al., 1990).

- *Polycythemia* due to increased erythropoietin production (Jacobs and Wood, 1994). More frequently, a high hematocrit is related to a shrunken plasma volume.
- *Renovascular hypertension*, usually by compression of the renal artery by a pheo (Gill et al., 2000). The diagnosis may be difficult, because high renin levels are often seen with a pheo (Plouin et al., 1988).
- *Adrenocortical hyperfunction*, which may arise from adrenocorticotropic hormone secretion from the pheo (Chen et al., 1995) or from a coincidental cortisol-secreting adenoma in the other adrenal (Ooi and Dardick, 1988) or bilateral hyperplasia (Amos and McRoberts, 1998). Hyperaldosteronism has been rarely noted (Tan et al., 1996).
- *Adrenocortical insufficiency*, which has been recognized in rare patients preoperatively and has been implicated in postoperative hypotension (Mulrow et al., 1959).
- *Rhabdomyolysis*, which has occurred with renal failure (Shemin et al., 1990).
- *Megacolon*, reported in 17 cases (Sweeney et al., 2000).

Conditions Simulating Pheochromocytoma

Most patients with hypertension and one or more of the manifestations of pheo turn out *not* to have that condition. Table 12-5 lists conditions that may simulate a pheo. Perhaps most common are repetitive episodes of acute anxiety or panic attacks that may induce both a hyperkinetic circulation and paroxysmal hypertension (Mann,1999). Some are associated with increased sympathetic activity from such diverse causes as baroreceptor dysfunction (Kuchel et al., 1987), central nervous system lesions (Wortsman et al., 1980), or drug interactions (Krentz et al., 2001; Lefebvre et al., 1995). On the other hand, increased thyroid function may be caused by a pheo, so the possibility should be considered before giving a b-blocker to control thyrotoxic symptoms (Ober, 1991).

Cardiovascular
Hyperdynamic, labile hypertension
Paroxysmal tachycardia
Angina, coronary insufficiency
Acute pulmonary edema
Eclampsia
Hypertensive crisis during or after surgery
Rebound hypertension after abrupt cessation of clonidine and other antihypertensives
Psychological
Anxiety with hyperventilation
Panic attacks
Neurologic
Migraine and cluster headaches
Brain tumor
Basilar artery aneurysm
Stroke
Dermatomal seizures
Porphyria
Lead poisoning
Familial dysautonomia
Acrodynia
Autonomic hyperreflexia, as with quadriplegia
Baroreceptor dysfunction
Fatal familial insomnia
Endocrine
Menopausal symptoms
Thyrotoxicosis
Diabetes mellitus
Hypoglycemia
Carcinoid
Mastocytosis
Drug-induced
Monoamine oxidase inhibitor + selective serotonin reuptake inhibitor
Ephedrine + tricyclic antidepressant
Fortuitous ingestion of sympathomimetics

TABLE 12-5. *Conditions that may simulate pheochromocytoma*

Pheochromocytoma during Pregnancy

The association of pheo and pregnancy may be greater than could be attributed to chance: More than 200 cases have been reported (Keely, 1998). When pheos are not recognized before delivery, the maternal mortality rate is approximately 25%, and the infant mortality rate is nearly 30%. If diagnosed during the first or second trimester, the pheo should be resected after the usual medical preparation (Finkenstedt et al., 1999). If diagnosed in the third trimester, medical therapy is usually preferred, with removal of the pheo at the time of elective cesarean section (Keely, 1998).

Pheochromocytoma in Children

The younger the patient, the more likely it is that the syndrome is familial, the pheos multiple and extraadrenal, and the hypertension persistent (Perel et al., 1997; Stackpole et al., 1963). The youngest patient in the series by Stackpole et al. (1963) was only 1 month old. Catecholamine-induced hypertension is also seen in approximately 20% of children with neurogenic tumors (Weinblatt et al., 1983).

Familial Syndromes

Nearly 10% of pheos are familial. These tumors are usually benign but are frequently associated with syndromes that include multiple other tumors (Hoff et al., 2000) (Table 12-6).

Type	Tumors (partial list)	Site of genetic mutations
Multiple endocrine neoplasia 2A	Medullary thyroid carcinoma Pheochromocytoma (50%) Hyperparathyroidism	Chromosome 10q11.2 codon 634, Cys→Arg in ~85%
Multiple endocrine neoplasia 2B	Medullary thyroid carcinoma Pheochromocytoma (50%) Mucosal neuromas	Chromosome 10q11.2 codon 918, Met→Thr in >95%
von Hippel-Lindau, type 2	Pheochromocytoma (25%) Retinal angioma Central nervous system hemangioblastoma Renal cysts and carcinoma Neuroendocrine tumors	Chromosome 3p25–26 codon 167 in ~40%
von Recklinghausen's disease (neurofibromatosis 1)	Neurofibroma Optic glioma Pheochromocytoma (5%) Carcinoid tumors	Chromosome 17q11.1 in 90%
Familial carotid body tumors	Paraganglioma	11q21–23

TABLE 12-6. *Familial syndromes with pheochromocytoma*

Familial pheos are often asymptomatic, and the majority of patients are young and normotensive, particularly when discovered as part of genetic screening of the family of an affected patient (Pomares et al., 1998). There is a greater likelihood of bilateral adrenal tumors: Fewer than 5% of sporadic cases but almost 50% of familial cases are bilateral.

Some of the same germline mutations in the RET proto-oncogenes present in the multiple endocrine neoplasia type 2 (MEN 2) syndromes have also been found in a few patients with sporadic pheos (Januszewicz et al., 2000). However, the genetic pathways involved in von Hippel-Lindau (VHL) pheos are distinct from those in sporadic pheos (Bender et al., 2000). Koper and Lamberts (2000) estimate that approximately 6% of sporadic pheos are in fact *de novo* manifestations of MEN 2 or VHL. They note that genetic mutation analyses on patients and their family are feasible with the MEN 2 syndrome because a limited number of mutations in the RET proto-oncogene are found with MEN 2. However, such analyses are more difficult with VHL-associated tumors because the affected gene is a tumor suppressor wherein any inactivating mutation may cause the syndrome.

Uncertainty remains about the treatment of familial syndromes (Walther, 2001). The following recommendations were agreed upon by the majority of experts at a 1998 workshop (Lips, 1998).

Multiple Endocrine Neoplasia Type 2

Family members of a patient with medullary thyroid cancer should have DNA diagnosis before age 10 and, if a germline RET gene mutation is found, total thyroidectomy should be done immediately. As for the diagnosis of pheo, plasma metanephrine levels should be measured every 6 months and an MRI obtained if levels are elevated (Eisenhofer et al., 1999, 2001). If a pheo is present in only one adrenal, unilateral adrenalectomy should be done. With bilateral tumors, found in

approximately half of the 50% of patients who develop a pheo, adrenal-sparing procedures should be attempted (Neumann et al., 1999).

von Hippel-Lindau Syndrome

In family members of patients with VHL syndrome, DNA analysis should be done before age 5. Given the markedly variable expressions of the VHL syndrome, with tumors reported in as many as 14 organs, diagnostic tests likely should be limited to MRI of the brain using gadolinium and plasma normetanephrine testing every year (Eisenhofer et al., 1999).

Because one-third of patients with VHL-pheos are asymptomatic and normotensive and have normal catecholamine levels (Eisenhofer et al., 2001), abdominal CT scanning and metaiodobenzylguanidine (MIBG) uptake should be done initially and repeated if catecholamine levels rise (Walther et al., 1999b). Laparoscopic partial adrenalectomy may be feasible (Walther et al., 2000).

von Recklinghausen's Disease

In a review of 118 articles, hypertension was noted in only approximately 2% of patients with von Recklinghausen's disease but, in those with hypertension, a pheo was identified in more than one-third (Walther et al., 1999a). In the 148 patients reported to have a pheo, their mean age was 42 years, 84% had a solitary adrenal tumor, 10% had bilateral adrenal tumors, and 6% had ectopic pheos. In 11.5%, the pheos were malignant, and 8.8% had coexisting gastrointestinal carcinoid tumors. Almost 80% of these patients had symptoms of pheo or hypertension and had increased catecholamine excretion and MIBG uptake.

Because pheos are relatively rare, only those with hypertension should have yearly urinary catecholamines and abdominal CT scans. Genetic testing of family members has little value.

Malignant Pheochromocytoma

As many as 10% of adrenal pheos and 40% of extraadrenal pheos are malignant (Najm et al., 1997). To be classified as malignant, metastases must be found in areas where chromaffin tissue normally is not located, because benign pheos often show dysplasia and invasion of capsule and vessel. Routine histology is of little value, and analysis of nuclear DNA content is not always helpful, because the normal diploid pattern has been seen in patients with invasive, malignant tumors (Heaney et al., 1996). Most metastases are to skeleton, lymph nodes, liver, and lungs. Tumor growth is often slow, and long survival is possible, likely enhanced by aggressive medical and surgical therapy, as will be described at the end of this chapter.

The diagnosis may be aided by the presence of large amounts of dopamine, recognized from its metabolite homovanillic acid in the urine or serum dopamine levels. Plasma chromogranin A levels may also be markedly elevated (Rao et al., 2000). The extent of metastatic disease may be determined by scintigraphy with radiolabeled MIBG or octreotide (Tenenbaum et al., 1995).

Death from Pheochromocytoma

Most deaths are related to failure to consider the disease in patients undergoing severe stress such as surgery or delivery. Many deaths are unexpected and sudden; this is likely related to catecholamine-induced effects on the cardiac muscle and conduction system. At least seven deaths have followed acute hemorrhagic necrosis of a pheo, most of them after phentolamine administration (van Way et al., 1976).

Biochemical Diagnosis

Routine laboratory screening for pheo in the workup of every hypertensive is not recommended. Testing should be reserved for patients with features suggestive of pheo (Table 12-4) or those with incidentally found adrenal masses. On the other hand, considering the potential for death from unrecognized pheos, screening tests must have virtually no false-negative results (i.e., must have near 100% sensitivity), even if there are some false-positive results (Pacak et al., 2001b).

Plasma Metanephrine

As seen in Table 12-7, measurement of plasma metanephrine and normetanephrine by liquid chromatography with electrochemical detection appears to be the most sensitive screening test for pheo (Eisenhofer, 2001), including those lesions found as part of familial syndromes (Eisenhofer et al., 1999; Pacak et al., 2001b; Raber et al., 2000a) or incidental adrenal masses (Raber et al., 2000b), and in interpretation of the clonidine suppression test (Eisenhofer et al., 2000). In the National Institutes of Health (NIH) experience, plasma metanephrines are elevated at least five times above normal in 82% of pheos, so that no further biochemical tests are usually needed (Eisenhofer, 2001).

Test	Normal range	Sensitivity (%)	Specificity (%)
Plasma			
Total catecholamines	85–501 pg/mL	85	98
Metanephrines	33–177 pg/mL	99	89
Urine			
Total catecholamines	15–100 μg/day	83	98
Vanillylmandelic acid	0–7.9 mg/day	83	94
Metanephrines	0–1.2 mg/day	76	94

Sensitivity was determined from tests in 151 patients with pheochromocytoma, specificity from 349 patients without pheochromocytoma.
Modified from Eisenhofer G. Biochemical diagnosis of pheochromocytoma. Ann Intern Med 2001;134:317–320.

TABLE 12-7. *Biochemical tests for pheochromocytoma*

Technique

Whereas levels of free catecholamines are increased by minimal anxiety or changes in posture, the levels of metanephrines should be much less affected and, therefore, less likely to give false-positive data (Raber et al., 2000a). Nonetheless, until there is more experience with plasma metanephrines, blood should be drawn from an indwelling catheter in place for at least 15 minutes and stored in ice until the plasma is separated and stored at –70°C or colder. The assay method is available online at http://www.catecholamine.org/ labprocedures and, hopefully, the assay will soon be more widely performed than just at the NIH or a few reference laboratories.

Acetaminophen interferes with the plasma normetanephrine assay (Lenders et al., 1993) and should be avoided for at least 5 days before sampling. Coffee should also be avoided for 1 day. According to Dr. Karel Pacak at the NIH, the intake of dibenzyline may also elevate plasma metanephrine levels, so blood should be obtained before the drug is given.

Rationale

The greater sensitivity and specificity for assays of plasma metanephrines has been explained by Eisenhofer et al. (1998). They found that the large amounts of membrane-bound catechol-Omethyltransferase in adrenal chromaffin cells have much higher affinity for catecholamines than does the soluble catechol-O-methyltransferase present elsewhere. Therefore, the adrenal glands contribute more than 90% of metanephrine (derived from Epi) and 24% to 40% of normetanephrine (derived from NE) in plasma, whereas only 7% of plasma NE comes from the adrenals, the rest from sympathetic nerves.

These investigators showed that the elevated plasma levels of free metanephrines in patients with pheo are derived from catecholamines produced and metabolized within the tumor. Whereas some tumors do not secrete catecholamines, they all metabolize the parent amines to free metanephrine (Fig. 12-2). This explains why some patients with a pheo have normal plasma Epi and NE levels but elevated metanephrines.

In most pheos, levels of both plasma free metanephrine and normetanephrine will be elevated, reflecting increased production of both Epi and NE, respectively. However, in most extraadrenal tumors only NE production is increased, because the phenylmethylamine N-methyl transferase enzyme needed for conversion of NE to Epi is lacking. For unknown reasons, only NE metabolites are elevated in most adrenal tumors associated with the VHL syndrome.

Urinary Tests

Until plasma metanephrine assays are more available, it may be easier and less expensive to measure spot urine samples for metanephrines as a screening test. As we noted (Kaplan et al., 1977) and others have confirmed (Ito et al., 1998), spot urine metanephrines, expressed as nanograms per milligram of creatinine, provide a sensitivity of 97% and specificity of close to 100% for diagnosing pheo, using a cutoff of 1,000 ng per mg creatinine.

Although other assays of urine catecholamines and their metabolites are still frequently performed (Table 12-7), they do not provide the sensitivity of plasma metanephrines (Lenders et al., 2000; Witteles et al., 2000).

Eisenhofer et al. (1999) explain the low sensitivity of urinary vanillylmandelic acid (VMA): Less than 20% of VMA comes from hepatic metabolism of circulating catecholamines and metanephrines, the remaining 80% from metabolites of NE from sympathetic neurons. Thus, to increase urinary VMA excretion from a pheo requires large increases in plasma catechols and metanephrines.

For a different reason, urine metanephrine assays are less sensitive than are plasma assays. The urinary metanephrine assay first hydrolyzes the 95% of metanephrines that are conjugated to sulfate before excretion. The sulfate-conjugated metanephrines are largely produced by sulfotransferase enzyme in the gastrointestinal tract whereas, as noted, the free metanephrines come directly from chromaffin tissue.

Interferences

With most plasma and urine assays but not with plasma metanephrines, levels of most catecholamines and metabolites may be elevated by the antihypertensive drugs labetalol (Feldman, 1987) and urapidil (Corcuff et al., 2000). A variety of other medications have been reported to alter measurements of catecholamines and metabolites (Young, 1997a) (Table 12-8).

Increase the values
Tricyclic antidepressants
Labetalol
Urapidil
Levodopa
Drugs containing catecholamines (e.g., decongestants)
Amphetamines, buspirone, and most psychoactive agents
Sotalol
Methyldopa
Withdrawal from clonidine hydrochloride (Catapres) and other drugs
Ethanol
Benzodiazepines
Acetaminophen
Decrease the values
Metyrosine
Methylglucamine[a]

[a]A component of iodinated contrast media that may cause metanephrine values to be falsely normal for as long as 72 hours when measured with Pisano's spectrophotometric method.

Modified from Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am 1997;26:801–827.

TABLE 12-8. *Medications that may alter measured levels of catecholamines and metabolites*

Patients taking sympathomimetic drugs likely will have elevated levels. Remember that patients under considerable stress (e.g., perioperatively, acute myocardial infarction or severe congestive heart failure) may have high catechol levels, and they should be tested only after the stress has subsided for 5 to 7 days.

Patients with End-Stage Disease

Patients with end-stage renal disease may be anuric, so urine measurements are not feasible. In end-stage renal disease patients on dialysis, plasma NE, dopamine, and metanephrine levels are usually elevated one- to twofold but rarely more than threefold, whereas plasma Epi levels are usually within normal limits (Godfrey et al., 2001). Plasma levels of any catecholamine in excess of threefold above normal are suggestive of pheo.

Chromogranin A Levels

Plasma chromogranin A levels are usually elevated in parallel with plasma NE levels but may be of additional value in identifying and following the course of malignant pheos (Rao et al., 2000) and in the presence of renal insufficiency (Canale and Bravo, 1994).

Pharmacologic Tests

Provocative Tests

In view of the availability of accurate plasma and urinary assays, there is little need to subject patients to the discomfort and hazard of provocative tests. At the Mayo Clinic, histamine and glucagon stimulation tests have been performed on 542 patients who were suspected of having a pheo, despite normal urinary tests; not one patient had a positive stimulation test (Young, 1997b).

The only rational use of the best of these pro-vocative procedures, the glucagon-stimulation test, is to identify bilateral medullary hyperplasia in patients with medullary carcinoma of the thyroid whose control urine metanephrine assays are normal or to diagnose a pheo in the extremely rare patient with normal plasma and urine catecholamine levels. However, it has proved insensitive in familial forms of pheo (Walther et al., 1999b). The safety of glucagon testing is improved by pretreatment with an a-blocker or a calcium channel blocker, neither of which blocks the rise in plasma catecholamines (Bravo, 1994).

Suppression Tests

Suppression tests, by nature, seem more physiologic and safer than provocative tests. The most widely used test uses the effect of the centrally acting sympathetic inhibitor clonidine on plasma catechols (Bravo et al., 1981). Plasma NE and Epi are measured before and 2 and 3 hours after a single oral 0.3-mg dose of clonidine; NE and Epi levels fall to less than the normal range in patients without a pheo but remain high in those with a pheo. A normal response (i.e., an absolute fall of plasma NE and Epi to less than 500 pg per mL and a relative fall of at least 40% from the basal level) was found in all 47 nonpheo hypertensives but in only 1 of 40 patients with a pheo (Bravo, 1994). The 2-hour sample almost always gives the best discrimination. To save money, the 3-hour sample can be frozen and analyzed only if the 2-hour sample is equivocal.

Much more accurate results have been found by the NIH investigators with measurement of plasma free metanephrines rather than catecholamines (Eisenhofer et al., 2000).

Summary of Biochemical Testing

The extensive experience of the NIH investigators in the diagnosis of pheo has been summarized by Eisenhofer (2001):

> Because of their uniquely high sensitivity, we recommend plasma metanephrines as the initial biochemical test. Since pheochromocytomas are rare, most tests will prove negative, reliably excluding pheochromocytoma so that no further tests are necessary. . . . Because the pretest probability of pheochromocytoma is very low, the incidence of false-positive results also has an important effect on diagnosis. As with all biochemical tests, high plasma levels of normetanephrine or metanephrine do not necessarily prove a pheochromocytoma. Thus, because of the low prevalence of pheochromocytoma, the number of false-positive results will probably far exceed the number of true-positive results. Nevertheless, at a 2% pretest probability of pheochromocytoma and at a specificity of 89%, a positive result on an initial test of plasma metanephrines increases the probability of pheochromocytoma to nearly 16%. . . . Our experience shows that more than 80% of patients with pheochromocytoma have [such markedly] elevated plasma metanephrine levels that indicate a pheochromocytoma with 100% specificity. For these patients, the probability of pheochromocytoma is increased to close to 100% by a single test of plasma metanephrines. The immediate task then is to localize the tumor by using imaging studies; further biochemical testing is not necessary.

In those with marginally elevated plasma metanephrines, Eisenhofer (2001) recommends these sequential steps:

- Exclude conditions or medications that might give false-positive results, including tricyclic antidepressants.
- Repeat plasma metanephrine and catecholamine tests.
- Perform the clonidine suppression test if plasma catechols are high.
- Perform the glucagon stimulation test if plasma catechols are normal.

LOCALIZING THE TUMOR

Only after biochemical studies have confirmed the diagnosis of a catecholamine-producing tumor should localization be attempted. Pacak and Goldstein (2001) have described their extensive experience at the NIH.

CT and MRI of the abdomen have simplified greatly the localization of pheos (Fig. 12-3). Most pheos are big enough (>2 cm) to be easily identified. Both CT and MRI provide high sensitivity, but approximately one-third of the abnormal scans will be nonpheo lesions, most an incidental adrenal tumor, as noted at the beginning of this chapter. CT and MRI can identify extraadrenal tumors and metastatic disease and have been of considerable help in evaluating patients with the MEN or VHL syndromes who may be normotensive and difficult to assess by biochemical tests.

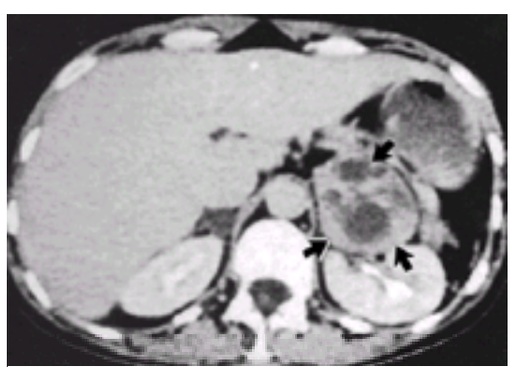

FIG. 12-3. Computed tomographic scan of a 40-year-old woman with a large left adrenal pheochro-mocytoma outlined by the arrows. Note the multiple cystic areas within the tumor.

In patients with abnormal hormonal tests but a negative CT or MRI, a ^{131}I-MIBG scan should be obtained. The NIH investigators recommend that an MIBG scan be done for confirmation even in those with a CT or MRI that shows a typical pheo. MIBG scans may also identify other neural crest tumors, including paragangliomas and schwannomas (Tommaselli et al., 1996). False-negative MIBG scans have been reported in patients with a pheo while taking labetalol, and interference with MIBG uptake has been reported with reserpine, calcium channel blockers, tricyclic antidepressants, and sympathomimetics (Khafagi et al., 1989). Scintigraphy with ^{123}I-MIBG, not available at present in the United States, provides even better detection of metastatic disease, particularly if supplemented by somatostatin receptor imaging (van der Harst et al., 2001).

If the results of abdominal CT or MRI and MIBG scanning are negative, Pacak and Goldstein (2001) recommend either continuous rotational or spiral CT for detecting small thoracic tumors or MRI for detecting juxtacardiac and juxtavascular pheos.

In the event that all of these are negative, positron emission tomography or, very rarely, multiple vena caval sampling for plasma catechols can be obtained in a center where such difficult cases are frequently evaluated (Pacak et al., 2001a).

MANAGEMENT

The symptoms of pheo can be controlled medically; but, if possible, surgery should be done with the expectation that all symptoms will be relieved in the majority of patients who have benign tumors and in the hope that metastatic spread will be limited in the minority with malignant ones. Although excellent results of surgery *without* preoperative a-blockade have been reported (Ulchaker et al., 1999), most authorities insist that the patient should be treated medically for at least 1 week, preferably until hypertension and spells are controlled (Prys-Roberts, 2000; Walther, 2001). In those who cannot be cured by surgery, medical therapy can be used chronically.

Benign Pheochromocytomas

Medical Therapy

In a hypertensive crisis, the a-adrenergic blocker phentolamine is given intravenously, 2 to 5 mg every 5 minutes, until the BP is controlled. If serious tachycardia or arrhythmias are present, a b-blocker may then be given intravenously. Control should be maintained by oral therapy until the patient is ready for surgery. Rarely, persistently lower BP has followed a-blocker therapy from hemorrhagic necrosis of the tumor (van Way et al., 1976).

A number of drugs that act in different ways can be used to prepare a patient for surgery or, if that is not feasible, to manage the disease in the long term (Shapiro and Fig, 1989) (Table 12-9).

Blockage of catecholamine receptor	α_1- and α_2-Blockers: phentolamine, phenoxybenzamine
	α_1-Blockers: doxazosin, prazosin, terazosin
	β-Blocker
Inhibition of catecholamine release	Calcium channel blockers
Inhibition of catecholamine synthesis	α-Methyl-para-tyrosine
Nonspecific cytotoxins	Chemotherapy: cyclophosphamide, vincristine, dacarbazine
Tissue-specific cytotoxins	6-OH-dopamine (not clinically applicable)

Adapted from Shapiro B, Fig LM. Management of pheochromocytoma. *Endocrinol Metab Clin North Am* 1988;18:443–461.

TABLE 12-9. *Pharmacotherapy of pheochromocytoma*

Nonselective a*-Blockers*

Oral phenoxybenzamine (dibenzyline) is the preferred nonselective a-blocker, because it has a smooth and prolonged action. The dose should be started at 10 mg once daily and increased slowly until the BP is at the desired level. Side effects, including postural hypotension, nasal stuffiness, fatigue, and inhibition of ejaculation, are rarely bothersome. Because the presynaptic a_2-receptor is also blocked by this drug, the release of NE from adrenergic neurons may increase, leading to tachycardia, which may call for the use of a b-blocker.

Selective a_1*-Blockers*

Oral prazosin, terazosin, or doxazosin will preferentially block the postsynaptic a_1-receptors on the vessel wall but will leave the presynaptic a_2-receptors on the neuronal surface open. Thus, the feedback inhibition of neuronal release of NE is preserved, unlike the situation with phenoxybenzamine. Tachycardia should be less of a problem, so that a b-blocker may not be needed (Prys-Roberts, 2000).

b-*Blockers*

b-Blockers may be given to control tachycardia and arrhythmias but *only* after a-blockers have been started. If inadvertently used alone, b-blockers may cause either a pressor response, because the b-blockade of the b_2-mediated vasodilator actions of Epi leaves the a-mediated vasoconstrictor actions unopposed, or pulmonary edema, presumably by removal of b-adrenergic drive to the heart (Prys-Roberts, 2000).

The combined a- and b-blocking drugs labetalol and carvedilol have been used with good results but only after the diagnostic tests are obtained: Recall the false-positive catecholamine assays from labetalol.

In rare patients whose disease cannot be controlled on any a-blocker (Hauptman et al., 1983), a calcium channel blocker may be effective (Ulchaker et al., 1999).

a-*Methyltyrosine*

An inhibitor of catecholamine synthesis, amethyl-*p*-tyrosine, or metyrosine (Demser), is available. Although effective, it may cause sedation, diarrhea, and other side effects. It should be used with an a-blocker, and the combination may be best of all (Steinsapir et al., 1997). Walther (2001) states that “the combination of metyrosine, phenoxybenzamine, a b-blocker, and liberal salt intake starting 10 to 14 days before surgery leads to better control of BP and decreases surgical risks.”

Surgical Therapy

Nonetheless, even with adequate preoperative control and intraoperative management, perioperative morbidity and mortality still occur (Plouin et al., 2001).

Anesthesia

Certain anesthetic agents have been advocated because they tend not to cause a release of catecholamines or to sensitize the myocardium. However, in the extensive experience of Prys-Roberts (2000), the type of anesthetic agent was of secondary importance to the control of operative hypotension by replacement of fluid volume and use of either phentolamine, labetalol, or nicardipine (Colson et al., 1998) to control hypertensive surges after tumor manipulation.

Surgical Procedure

In the past, most surgeons preferred an upper abdominal incision long enough to expose both adrenals, the entire periaortic sympathetic chain, and the urinary bladder. Although only one pheo may be found, exploration must be thorough, because as many as 20% of patients have multiple pheos, particularly in familial cases.

The need for such extensive exploration is less likely with the availability of CT and MRI scans. With accurate localization of a unilateral tumor, a flank extraperitoneal approach (Obara et al., 1995) and, increasingly, laparoscopy have been used (Walther et al., 2000), but catechola-mine release may occur as with other procedures (Joris et al., 1999).

After removal of the pheo, the BP may fall precipitously for one or more reasons (Fig. 12-4). The principal factor seems to be the shrunken blood volume, which is no longer supported by intense vasoconstriction.

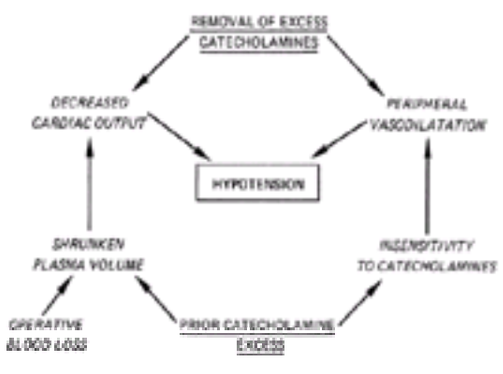

FIG. 12-4. Possible causes of hypotension after removal of a pheochromocytoma.

Postoperative Care

Patients may become hypoglycemic in the immediate postoperative period, presumably because the sudden decrease in catecholamines leads to an increase in insulin secretion while simultaneously decreasing the formation of glucose from glycogen and fat.

If the pressure remains high, some of the tumor may have been inadvertently left behind. Less commonly, a renal artery may have been damaged, with induction of renovascular hypertension. The presence of residual tumor can be checked by the response to intravenous phentolamine, but reexploration should await repeated urine collection for catecholamine measures and appropriate imaging or scintigraphy.

Long-Term Follow-Up

The prognosis is usually excellent for benign pheos, although recurrences were noted over a 10-year follow-up in 16 of 114 patients with a benign pheo at initial operation (Plouin et al., 1997). Moreover, of the 98 patients alive without recurrence, only 48 were normotensive at their most recent follow-up. If the pheo is not totally resectable or the patient is a high surgical risk, long-term medical therapy can provide excellent control of all pheo manifestations (Pelegri et al., 1989). If the

patient has one of the familial syndromes described earlier in this chapter, repeated catechol assays in conjunction with blood calcitonin levels and palpation of the neck for medullary thyroid cancer should be continued for life.

Malignant Pheochromocytomas

The prognosis is obviously not as good for those with metastatic disease. As much tumor mass as can be reached should be resected, and medical therapy should be provided to shrink the tumor and control the symptoms. Shrinkage of tumor mass has been reported with metyrosine (Serri et al., 1984), streptozocin (Feldman, 1983), and ^{131}I-MIBG and chemotherapy (Sisson et al., 1999); skeletal metastases may respond to irradiation (Scott et al., 1982). The best response has been reported with chemotherapy combining cyclophosphamide, vincristine, and dacarbazine (Averbuch et al., 1988; Tato et al., 1997). Long-term control of symptoms is possible with a- and b-blockers and metyrosine. With such aggressive therapy, long-term survival is possible. The response to therapy may be gauged by levels of plasma chromogranin A (Rao et al., 2000).

We next examine primary aldosteronism, another fascinating adrenal cause of hypertension that may be more common than was previously thought.

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13
Primary Aldosteronism

Interest in primary aldosteronism has heightened over the last few years, with increasingly easier recognition of milder presentations of the classic syndrome (Stowasser, 2001) and elucidation of the pathophysiology of two relatively rare but fascinating forms of mineralocorticoid excess: glucocorticoid-remediable aldosteronism (GRA) (Lifton et al., 1992) and apparent mineralocorticoid excess (Ulick, 1991).

This chapter covers those syndromes listed in Table 13-1 in which secretion of the physiologic mineralocorticoid aldosterone is primarily increased. The next chapter covers syndromes caused by increased secretion of other mineralocorticoids (e.g., congenital adrenal hyperplasias) or by cortisol acting on mineralocorticoid receptors (e.g., apparent mineralocorticoid excess).

Adrenal origin
Aldosterone excess (primary)
Aldosterone-producing adenoma
Bilateral hyperplasia
Primary unilateral adrenal hyperplasia
Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism type I)
Adrenal carcinoma
Extraadrenal tumors
Deoxycorticosterone excess
Deoxycorticosterone-secreting tumors
Congenital adrenal hyperplasia
11β-Hydroxylase deficiency
17α-Hydroxylase deficiency
Cortisol excess
Cushing's syndrome from adrenocorticotropic hormone–producing tumor
Glucocorticoid receptor resistance
Renal origin
Activating mutation of mineralocorticoid receptor
Pseudohypoaldosteronism type II (Gordon's)
11β-Hydroxysteroid dehydrogenase deficiency
Congenital: apparent mineralocorticoid excess
Acquired: licorice, carbenoxolone

TABLE 13-1. *Syndromes of mineralocorticoid excess*

As milder degrees of primary aldosteronism have been recognized by the wider application of a simple screening test, the aldosterone-renin ratio (ARR), it has become abundantly clear that the majority of patients with a positive screening test do not have a solitary adrenal adenoma by computed tomography (CT) or magnetic resonance imaging (MRI) (Magill et al., 2001; Rossi et al., 2001). Therefore, bilateral adrenal venous sampling (AVS), a procedure that requires considerable expertise in performance and, even in the best of circumstances, is only 80% conclusive, is now being advocated for confirmation of the type of pathology (Magill et al., 2001; Phillips et al., 2000; Rossi et al., 2001).

The need to establish the type of pathology is critical: Adenomas usually should be surgically removed; bilateral hyperplasia should never be surgically attacked but will almost always respond to medical therapy (Lim et al., 2001).

The clinician is left in a dilemma: As the diagnosis of primary aldosteronism has become easier, the recognition of the type of pathology has become more difficult. Because CT and MRI often are inadequate and AVS requires considerable expertise, patients may often need referral to a center experienced in definitive testing.

To avoid this dilemma, this text presents a more conservative view: Screening for aldosteronism should not be done except in patients with unexplained hypokalemia or resistance to triple-drug therapy. Even if primary aldosteronism is thereby missed, medical therapy—usually including the aldosterone receptor blocker spironolactone— will almost always control the hypertension and, if present, the hypokalemia. Thereby, the patient will be protected and, at the same time, expensive laboratory procedures, invasive diagnostic tests, and unnecessary surgery will be avoided.

This view, which will be detailed in the remainder of this chapter, may be too conservative. However, as of now, it seems to be the best balance between the multiple costs of diagnosis and the major benefits of specific therapy.

DEFINITIONS

Primary aldosteronism is the syndrome resulting from the autonomous hypersecretion of aldosterone, almost always from the adrenal cortex, usually by a solitary adenoma or by bilateral hyperplasia, rarely by variants of these two (Stewart, 1999) (Table 13-1).

Most aldosteronism seen in clinical practice is *secondary* to an increase in renin-angiotensin activity. A classification of the various forms of secondary aldosteronism by mechanism is virtually the same as the list of conditions that cause increased plasma renin activity (PRA), which appears in Table 3-5. The ability to measure PRA has made the differentiation much easier, because renin is elevated in secondary aldosteronism and suppressed in primary aldosteronism.

INCIDENCE

Soon after the first cases were described, apparently by a Polish physician writing in an obscure journal (Litynski, 1953), Conn (1955) fully characterized the

fascinating syndrome of primary aldosteronism. Over the next decade, Conn et al. (1965) broadened the scope of this condition so that it covered almost 20% of the hypertensive patients at the University of Michigan. This high prevalence was subsequently shown to reflect the nature of the patients referred to that center, highly selected and suspected of having the disease. In most series of unselected patients, classic primary aldosteronism was found in fewer than 0.5% of hypertensives (Gifford, 1969; Kaplan, 1967; Sinclair et al., 1987). Throughout Denmark from 1977 to 1981, only 19 cases were identified, corresponding to 0.8 cases per million people per year (Andersen et al., 1988). During the same period, 47 cases of pheochromocytoma were identified.

On the other hand, using a relatively simple screening test—the ARR—one group of investigators in Brisbane, Australia, have found almost 100 patients with primary aldosteronism per year (Gordon et al., 2001). Others have found an abnormal ARR in 4% to 32% of hypertensives (Stowasser, 2001) but, as I will argue later, that alone does not establish the diagnosis. Although the incidence of primary aldosteronism may be higher than previously was thought, it is very unlikely to be as common as some now believe (Kaplan, 2001).

CLINICAL FEATURES

The disease is usually seen in patients between the ages of 30 and 50 years, although cases have been found in patients from age 3 to 75, and in women more frequently than in men. The syndrome has been recognized during pregnancy in hypokalemic patients with even higher aldosterone levels than expected and, most important, suppressed PRA (Solomon et al., 1996).

The classic clinical features of primary aldosteronism are hypertension, hypokalemia, excessive urinary potassium excretion, hypernatremia, and metabolic alkalosis (Fig. 13-1). The usual presence of these features reflects the pathophysiology of aldosterone excess.

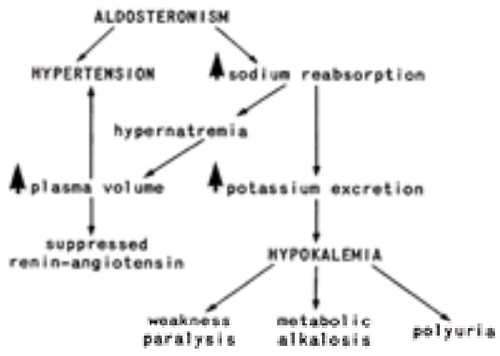

FIG. 13-1. Pathophysiology of primary aldosteronism. (Reprinted from Kaplan NM. Primary aldosteronism. In: Astwood EB, Cassidy CE, eds. *Clinical endocrinology*, vol 2. New York: Grune & Stratton, 1968:468–472, with permission.)

Hypertension

Patients with primary aldosteronism are hypertensive, with few exceptions (Suzuki et al., 1999; Vantyghem et al., 1999). The blood pressure (BP) may be quite high: The mean in one series of 136 patients was 205/123 mm Hg (Ferriss et al., 1978b). In another series of 140 patients, 28 had severe, resistant hypertension (Bravo et al., 1988). More than a dozen patients have had malignant hypertension (Kaplan, 1963; Zarifis et al., 1996). Unlike the high renin levels seen with other causes of malignant hypertension, renin levels are low in those who have primary aldosteronism (Wu et al., 2000).

Complications

High prevalences of left ventricular hypertrophy and myocardial ischemia (Napoli et al., 1999), cerebrovascular disease, and renal insufficiency (Nishimura et al., 1999) have been noted in patients with classic primary aldosteronism. Aldosterone exerts rapid, nongenomic effects through its interaction with the mineralocorticoid receptor (Tao et al., 2000), which lead to vascular damage (Duprez et al., 2000) and stimulate fibrosis in the heart (Weber, 2000) and kidney (Ciraku et al., 2000), so these pathologies may reflect more than the accompanying hypertension. Moreover, aldosterone may be synthesized in the heart (Takeda et al., 2000), providing a direct path to cardiac pathology.

Hemodynamics

The hypertension is hemodynamically characterized by a slightly expanded plasma volume, an increased total body and exchangeable sodium content, and an increased peripheral resistance (Bravo, 1994; Williams et al., 1984). When ten patients with primary aldosteronism, previously well controlled on spironolactone, were studied 2 weeks after the drug was stopped and the hypertension reappeared, cardiac output and sodium content (both plasma volume and total exchangeable sodium) rose initially (Wenting et al., 1982) (Fig. 13-2). Between weeks 2 and 6, the hemodynamic patterns separated into two types: In five patients, the hypertension was maintained through increased cardiac output; in the other five, cardiac output and blood volume returned to their initial values, but total peripheral resistance rose markedly. Total body sodium space remained expanded in both groups, although more so in those with increased cardiac output (Man in't Veld et al., 1984). After surgery, the cardiac output fell in the high-flow patients, and the peripheral resistance fell in the high-resistance patients.

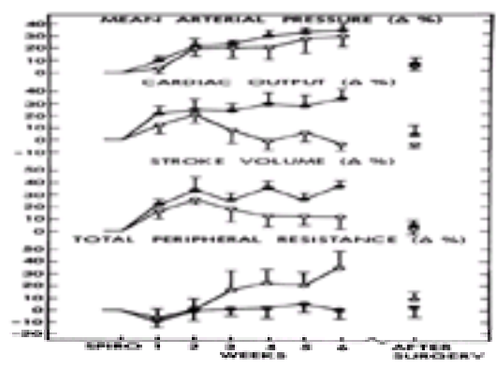

FIG. 13-2. Changes (mean ± standard error of the mean) in systemic hemodynamics after discontinuation of spironolactone treatment (SPIRO) and after surgery in ten patients with primary aldosteronism. Note the fall in stroke volume and cardiac output after 2 weeks in the five patients with high-resistance hypertension (*open circles*) as compared to the five with high-flow hypertension (*closed circles*). (Reprinted from Wenting GJ, Man in't Veld AJ, Derkx FHM, Schalekamp MADH. Recurrence of hypertension in primary aldosteronism after discontinuation of spironolactone. Time course of changes in cardiac output and body fluid volumes. *Clin Exp Hypertens* 1982;A4:1727– 1748, with permission.)

Mechanism of Sodium Retention

The pressor actions of aldosterone are generally related to its effects on sodium retention via its action on renal mineralocorticoid receptors. The human kidney mineralocorticoid receptor has been cloned, sequenced, expressed, and shown to be equally receptive to glucocorticoids and to mineralocorticoids (Arriza et al., 1987; Farman and Rafestin-Oblin, 2001). Relatively small concentrations of aldosterone are able to bind to the mineralocorticoid receptor in the face of much higher concentrations of glucocorticoids (mainly cortisol) because of the action of the 11b-hydroxysteroid dehydrogenase enzyme, which converts the cortisol (with its equal

affinity) into cortisone, which does not bind to the receptor (Walker, 1993).

Aldosterone stimulates sodium reabsorption through complex genomic effects that collectively act to increase the activity of the epithelial sodium channel in the apical membrane (Stokes, 2000). After a certain amount of volume expansion, the increase in renal perfusion pressure in some way leads to a decrease in abundance of the thiazide-sensitive Na-Cl cotransporter of the distal convoluted tubule so that “escape” from progressive sodium retention occurs, despite continued aldosterone excess (Wang et al., 2001).

Hypokalemia

Incidence

Originally, persistent normokalemia was rarely seen (Conn et al., 1965). In the Medical Research Council series, hypokalemia occurred in all 62 patients with a proven adenoma and was persistent in 53; among the 17 with hyperplasia, plasma potassium was persistently normal in only three patients (Ferriss et al., 1983). Subsequently, approximately 20% of patients with a functional adenoma were found to have a low-normal serum potassium, perhaps because they have been on a low-sodium diet, which limits potassium wastage by decreasing sodium delivery to the distal tubule (Ganguly, 1998). Most recently, patients identified by the finding of an elevated ARR are normokalemic (Stowasser, 2000), which could reflect either the possibility that they do not have aldosterone excess or the presence of bilateral hyperplasia, wherein potassium wastage is less than with an adenoma.

Patients with GRA are often normokalemic, attributable to their mild degree of hyperaldosteronism with minimal potassium wasting (Litchfield et al., 1997).

Significance

Although persistent hypokalemia appears to be less common in patients in whom adenoma is diagnosed early in its course, the argument can be made that the search for primary aldosteronism need be undertaken only in those with hypokalemia or other suggestive features (Stewart, 1999). The few who might initially be missed because of a normal potassium level will likely show up subsequently with diuretic-induced or spontaneous hypokalemia. In the interim, a few patients may have a delay in their diagnosis, but many more will be saved the expense and discomfort of unnecessary workups. On the other hand, in hypertensives with *unprovoked* hypokalemia, perhaps half will turn out to have primary aldosteronism; thus, they must have a complete evaluation.

Mechanism

Considering the effects of persistent aldosterone excess, hypokalemia is certainly to be expected. Whereas with continued exposure to excessive mineralocorticoids the renal retention of sodium escapes, the renal wastage of potassium is unrelenting (Giebisch, 1998). The aldosterone-driven increase in potassium secretion also involves an exchange of hydrogen for sodium, so that metabolic alkalosis is generated; increased proximal and distal reabsorption of bicarbonate maintains the alkalosis, the severity of which is related to the degree of hypokalemia.

Consequences

The effects of hypokalemia include easy fatigability and muscle weakness, even progressing to paralysis (Huang et al., 1996); polyuria from a loss of renal-concentrating ability; a high incidence of renal cysts (Torres et al., 1990); increased ventricular ectopy; blunting of circulatory reflexes with postural falls in pressure without compensatory tachycardia; impaired insulin secretion with decreased carbohydrate tolerance (Shimamoto et al., 1994); and suppression of aldosterone synthesis, even from presumably autonomous adenomas (Kaplan, 1967). Beyond these rather obvious effects, chronic potassium depletion may accelerate atherosclerosis and vascular injury (Young and Ma, 1999).

Suppression of Renin Release

As a consequence of the initial expansion of vascular volume and the elevated BP, the baroreceptor mechanism in the walls of the renal afferent arterioles suppresses the secretion of renin (Conn et al., 1964) to the point that renin messenger RNA may be undetectable in the kidney (Shionoiri et al., 1992). Patients with primary aldosteronism almost all have low levels of PRA that respond poorly to upright posture and diuretics, two maneuvers that usually raise PRA (Hirohara et al., 2001). Rarely, concomitant renal damage may stimulate renin release (Oelkers et al., 2000).

Other Effects

- Hypernatremia is usual, unlike most forms of edematous secondary aldosteronism, in which the sodium concentration is often quite low, or with diuretic-induced hypokalemia, in which a slightly low serum sodium is usually found; thus the serum sodium concentration provides a useful clinical hint which differentiates primary and secondary aldosteronism.
- Hypomagnesemia from excessive renal excretion of magnesium may produce tetany.
- Sodium retention and potassium wastage may be demonstrable wherever such exchange is affected by aldosterone: sweat, saliva, and stool.
- Atrial natriuretic peptide levels are appropriately elevated for a state of volume expansion as shown by Opocher et al. (1992).

DIAGNOSIS

The diagnosis of primary aldosteronism should be easy to make in patients with unprovoked hypokalemia and other manifestations of the fully expressed syndrome. Unprovoked hypokalemia must be thoroughly evaluated, by following the scheme shown in Figure 13-3. Although a surprisingly high prevalence of possible primary aldosteronism has been uncovered in unselected, normokalemic hypertensives by the use of the ARR (Gordon et al., 2001; Stowasser, 2001), I believe the ratio should not be performed as a routine procedure. Admittedly, the fact that hypokalemia is usually present in most patients in large series may reflect the failure to look for the syndrome in normokalemic hypertensives. Obviously, the ARR provides much more sensitive screening, perhaps uncovering subclinical cases that might never proceed into the full syndrome (Massien-Simon et al., 1995).

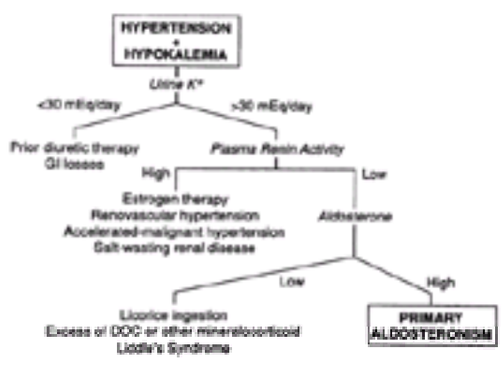

FIG. 13-3. Flow diagram for the differential diagnosis of hypertension with hypokalemia. DOC, deoxycorticosterone; GI, gastrointestinal; K^+, potassium.

To reduce unnecessary laboratory costs, I measure plasma aldosterone and renin activity only in the following cases:

- In patients with unexplained hypokalemia.
- In patients with hypokalemia induced by diuretics but resistant to correction.
- In hypertensive family members of patients with familial aldosteronism.

- In some patients with hypertension that is difficult to control.

For most hypertensive patients, the plasma potassium remains an adequate screen.

Screening Tests

Plasma Potassium

Caution should be used to ensure that hypokalemia is not inadvertently missed. A number of factors may cause a temporary and spurious rise in plasma potassium (Wiederkehr and Moe, 2000), including

- A difficult and painful venipuncture, which causes plasma potassium to rise for multiple reasons: If the patient hyperventilates, the respiratory alkalosis causes potassium to leave cells; repeated fist clenching causes potassium to leave the exercising muscles; if the tourniquet is left on, plasma potassium rises from venous stasis.
- Any degree of hemolysis.
- Efflux of potassium from blood cells if separation of plasma by centrifugation is delayed or if the sample is placed on ice.
- Release of potassium from red cells during clot formation if serum is analyzed, raising the average level by 0.2 mmol per L (Hyman and Kaplan, 1985).
- Efflux of potassium into plasma from elevated numbers of white cells or platelets.

Urinary Potassium

If hypokalemia is present, a 24-hour urine sample should be collected for sodium and potassium levels before starting potassium-replacement therapy and 3 to 4 days after diuretics have been stopped. If the urinary sodium exceeds 100 mmol per 24 hours (to ensure that enough sodium is present to allow potassium wastage to express itself), the presence of a potassium level higher than 30 mmol per 24 hours indicates a driven wastage of potassium through the kidneys. In addition to the action of excess mineralocorticoid in the syndromes of primary aldosteronism, a number of other conditions may require consideration, conditions in which hypokalemia is coupled with renal potassium wastage (Table 13-2). If the urinary potassium is less than 30 mmol per 24 hours, mineralocorticoid excess is much less likely, and other causes of hypokalemia may be responsible (Table 13-3).

High flow rate of potassium in the cortical collecting duct (CCD)
Increased sodium excretion (e.g., diuretics)
Increased organic osmoles
Glucose
Urea
Mannitol
High potassium concentration in the CCD
With expanded intravascular volume (low plasma renin)
Primary mineralocorticoid excess (see Table 13-1)
Liddle's syndrome
Amphotericin B
With contracted intravascular volume (high plasma renin)
Bartter's syndrome
Gitelman's syndrome
Magnesium depletion
Increased bicarbonate excretion
Secondary aldosteronism (e.g., nephrotic syndrome)

TABLE 13-2. *Causes of hypokalemia due to renal loss of potassium*

Prior diuretic use
Cellular shifts
Rapid tumor growth
Alkalosis (e.g., hyperventilation)
Hormones, insulin, β-agonists
Periodic paralysis
Decreased intake: starvation
Increased nonrenal loss
Gastrointestinal system
Vomiting and drainage
Diarrhea and laxatives
Skin
Sweating
Burns

TABLE 13-3. *Causes of hypokalemia without urinary potassium wastage*

If the collection of a 24-hour urine sample is difficult, measurement of either the fractional excretion of potassium or the transtubular potassium gradient in a single voided specimen will separate renal from nonrenal causes of hypokalemia (Halperin and Kamel, 1998).

Once the renal origin of hypokalemia is recognized, it may be preferable to correct the hypokalemia with potassium supplements, 40 to 80 mmol per day, after discontinuation of diuretics and before performing additional workup. To restore total body potassium deficits after prolonged diuretic use, a minimum of 3 weeks is needed, and it may take months. After a suitable interval, the supplemental potassium should be stopped for at least 3 days, and the plasma potassium level should be rechecked. If plasma potassium is normal, plasma renin and aldosterone levels should be measured.

In practice, a more rapid screening protocol may be used: Once hypokalemia is recognized, measure the plasma aldosterone and PRA. If the plasma aldosterone is elevated and the PRA suppressed, the diagnosis of primary aldosteronism is strongly supported. However, hypokalemia will suppress aldosterone secretion even from an adenoma, so the plasma aldosterone may not be elevated. As a reasonable compromise, the blood for renin and aldosterone could be drawn, the plasma separated and frozen, and the analyses done only if the 24-hour urine sample displays excessive potassium wastage. Regardless, if the plasma aldosterone is not definitely abnormal in the presence of hypokalemia, it may need to be repeated after potassium replenishment.

Plasma Aldosterone-Renin Ratio

Plasma aldosterone and plasma renin activity are measured in a peripheral venous blood sample, preferably obtained while the patient is on no antihypertensive drugs and without prior manipulation of diet (Hiramatsu et al., 1981). The values are put into a ratio, dividing the plasma aldosterone activity (normal, 5 to 20 ng per dL) by the PRA (normal, 1 to 3 ng per mL per hour). The normal ratio would be approximately 10, whereas in patients with primary aldosteronism it is almost always well above 20 and usually higher than 50 (Hirohara et al., 2001; Kaplan, 2001). If plasma aldosterone is measured in picomoles per liter, an abnormal ratio would exceed 900.*

As seen in Figure 13-4, this simple procedure has proved to be quite useful as a screening test (Ignatowska-Świtalska et al., 1997; Loh et al., 2000; McKenna et al., 1991; Weinberger and Feinberg, 1993). In the series by McKenna et al. (1991), the only patients with a high ratio who did not have primary aldosteronism were 5 of 17 patients with chronic renal failure, in whom PRA was suppressed by loss of juxtaglomerular cells and hypervolemia and plasma aldosterone was elevated by hyperkalemia. Because plasma aldosterone levels in patients with aldosteroneproducing adenomas (APAs) usually fall during the day in concert with adrenocorticotropic hormone (ACTH) and cortisol (Siragy et al., 1995), the blood sample should be obtained early in the morning, if possible. The ratio may increase in response to upright posture (Montori et al., 2000) or a high sodium intake (He et al., 2000).

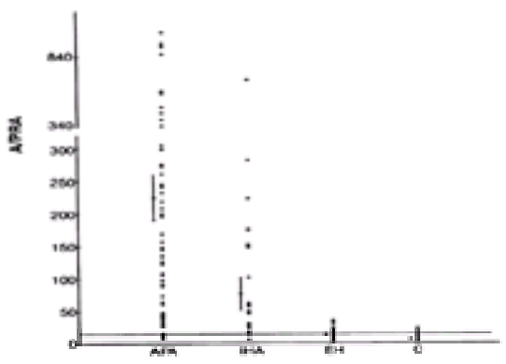

FIG. 13-4. Individual aldosterone– plasma renin activity (A/PRA) or aldosterone-renin ratio in 74 patients with aldosterone-producing adenoma (APA), 29 with idiopathic bilateral hyperplasia (IHA), 31 with essential hypertension (EH), and 45 normotensive controls (C). The aldosterone levels are in nanograms per deciliter, the PRA in nanograms per milliliter per hour. The upper limit of normal was 17.8 based on the mean ± 2 standard deviations in the control subjects. (Reprinted from Ignatowska-Świtalska H, Chodakowska J, Januszewicz W, et al. Evaluation of plasma aldosterone to plasma renin activity ratio in patients with primary aldosteronism. *J Hum Hypertens* 1997;11: 373–378, with permission.)

Caution in interpreting the ARR is needed in two regards. First, many patients with primary hypertension, particularly elderly and black individuals, have low PRA levels, so that a high ARR can simply reflect the low PRA with normal aldosterone secretion. Therefore, the plasma aldosterone level should be *above normal* to signify a truly high ratio. Second, drugs may interfere, some raising even suppressed PRA levels (diuretics, spironolactone, angiotensin-converting enzyme inhibitors), others lowering elevated PRA levels (b-blockers), and others raising plasma aldosterone levels (spironolactone). Therefore, if possible, the ARR should be obtained in the absence of antihypertensive drugs. Nonetheless, in one series of 90 patients, the ARR gave expected results, despite various concomitant antihypertensive drug therapies (Gallay et al., 2001).

An elevated ARR has been found in many more hypertensives than the 0.5% to 1.0% prevalence previously accepted. Gordon and colleagues in Brisbane, Australia, were the first to recommend it as a routine test (Hamlet et al., 1985), subsequently reporting 8.5% of normokalemic hypertensives to have an elevated ARR (Gordon et al., 2001). Others have reported an elevated ARR in presumably unselected hypertensive patients from 2.7% (Brown et al., 1996) to as high as 18% (Loh et al., 2000) and, in referred, resistant hypertensives, as high as 32% (Rayner et al., 2000). Most of these were normokalemic.

Caution is advised before accepting these high figures (Kaplan, 2001), because in only one report (Hiramatsu et al., 1981) has the diagnosis of hyperaldosteronism been established in more than a small minority of those with an elevated ARR. For example, 77 of 495 patients were found to have an elevated ARR, but only 5 of the 77 were reported to have an APA (Lim et al., 2000a). Most patients with an elevated ARR who have hyperaldosteronism likely have bilateral hyperplasia, so surgery would not be indicated and they can successfully be treated medically. I now agree with Stewart (1999): The ARR is not a suitable screening test because it primarily reflects a low level of PRA (Montori et al., 2001). The ARR became popular because it is so simple, but blind use of the ARR can be misleading. Rather than using a potentially misleading ratio, clinicians should simply look at the plasma aldosterone and PRA levels: If the plasma aldosterone is high and the PRA suppressed, the patient should be further evaluated for primary aldosteronism.

Confirmatory Tests

If the plasma aldosterone is high and the PRA low, some would proceed to CT or MRI of the adrenal glands. However, as shown in Figure 13-5, more definitive proof of the presence of primary aldosteronism should be obtained before proceeding to the more expensive scans, particularly because the scans may be either falsely negative, missing perhaps 10% of adrenal abnormalities, or falsely positive, finding incidental adrenal masses, as described at the beginning of Chapter 12. Nonetheless, if the scan shows a definite lesion in the presence of unprovoked hypokalemia and a high plasma aldosterone and low PRA, the rest of the confirmatory tests may be superfluous, and only additional definition of the type of adrenal pathology may be needed.

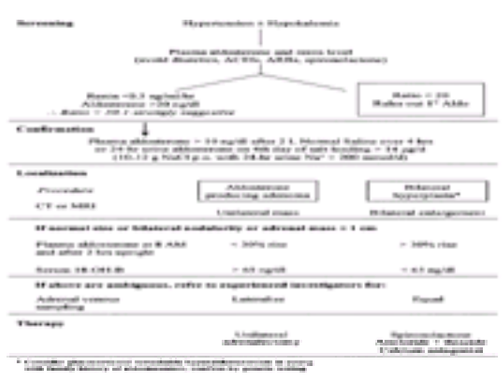

FIG. 13-5. A diagnostic flow chart for evaluating and treating patients with primary aldosteronism. 1° Aldo, primary aldosteronism; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II–receptor blocker; CT, computed tomography; MRI, magnetic resonance imaging; 18-OH-B, 18-hydroxycorticosterone. *Consider glucocorticoid remediable hyperaldosteronism in young with family history of aldosteronism; confirm by genetic testing.

Elevated and Nonsuppressible Aldosterone

Saline Suppression

One way to document that aldosterone levels are elevated and do not suppress normally is by the saline suppression test (Kem et al., 1971). Plasma aldosterone is measured before and after the infusion of 2 L normal saline over 4 hours. Patients with primary aldosteronism have higher basal levels but, more important, fail to suppress these levels after saline to less than 10 ng per dL. Some patients with adrenal hyperplasia may suppress to a level between 5 and 10 ng per dL after saline, so that the normal level may need to be set at 5 ng per dL when screening is done for hyperplasia (Holland et al., 1984).

Others prefer to measure urinary aldosterone levels after 3 days of oral sodium loading, with an abnormal level being in excess of 12 (Young, 1997) or 14 µg per 24 hours (Bravo, 1994). In the Cleveland Clinic series, this was the most sensitive test (Bravo, 1994) but was falsely normal in 7 patients subsequently found to have primary aldosteronism (Bravo, 1995).

Captopril Suppression

Whereas plasma aldosterone levels were markedly suppressed 3 hours after oral intake of 1 mg captopril per kilogram of body weight in patients with essential hypertension or renovascular hypertension, they remained elevated in patients with primary hyperaldosteronism (Thibonnier et al., 1982). The presence of an ARR higher than 30 both before and 90 minutes after 50 mg captopril has been reported to be a useful confirmatory test (Rossi et al., 1996).

Response to Spironolactone

Spark and Melby (1968) showed that patients with primary aldosteronism had a fall of at least 20 mm Hg in their diastolic BP after 5 weeks of spironolactone, 100 mg

four times a day. Although the procedure is no longer needed as a diagnostic test, the response to spironolactone may have prognostic value, because the response to spironolactone in patients with an adenoma closely resembled their subsequent response to surgery (Ferriss et al., 1978a).

Ruling Out Glucocorticoid-Remediable Aldosteronism

As will be described in the next section, GRA should be considered in the absence of an adenoma, particularly if other family members have aldosteronism. This is most easily confirmed by demonstrating the hybrid gene in a blood sample, as noted later in this chapter.

18-Hydroxycorticosterone

The precursor of aldosterone, 18-hydroxycorticos-terone (18-OH-B), may be elevated even more than the aldosterone level (Biglieri and Schambelan, 1979). Serum levels are useful both in establishing the diagnosis and in separating the two major types of adrenal pathology, as shown in Figure 13-5 and as discussed later in this chapter.

Excluding Other Diseases

Various causes of secondary aldosteronism are easily excluded by the presence of edema and high levels of peripheral blood PRA. In addition, there are a number of inherited renal tubular disorders, some associated with hypertension and hypokalemia, that should not be confused with primary aldosteronism (Scheinman et al., 1999) (Table 13-4). Other disorders are associated with either hyperkalemia or normotension, so the distinction should be obvious.

Disorder	Inheritance	Consequences of mutant gene
Hypertension and hypokalemia		
Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism type I)	Dominant	Increased mineralocorticoids from chimeric 11b-hydroxylase and aldosterone synthase genes
Apparent mineralocorticoid excess	Recessive	Reduced inactivation of cortisol due to 11b-hydroxysteroid dehydrogenase deficiency
Mutation of mineralocorticoid receptor	Dominant	Increased activity of mineralocorticoid receptor
Liddle's syndrome	Dominant	Increased activity of epithelial sodium channel
Hypertension and hyperkalemia		
Pseudohypoaldosteronism type II (Gordon's syndrome)	Dominant	Increased chloride reabsorption in distal tubule
Normotension and hypokalemia		
Bartter's syndrome	Recessive	Decreased sodium chloride reabsorption in thick ascending Henle's loop (three types of defect)
Gitelman's syndrome	Recessive	Decreased sodium chloride cotransport in distal convoluted tubule
Normotension and hyperkalemia		
Pseudohypoaldosteronism type I	Recessive Dominant	Reduced activity of epithelial sodium channel Reduced activity of mineralocorticoid receptor

TABLE 13-4. *Inherited renal tubular disorders*

Those conditions listed in the preceding sections, Hypertension and Hypokalemia, also have suppressed, low PRA, but all have low aldosterone levels, because of the secretion of other mineralocorticoids (glucocorticoid-remediable hyperaldosteronism, to be covered later in this chapter), because of increased cortisol acting as a mineralocorticoid (apparent mineralocorticoid excess, to be covered in Chapter 14), because of increased sodium reabsorption from activated sodium channels (Liddle's syndrome), or because of increased activity of mineralocorticoid receptors (Geller et al., 2000).

Excessive Renal Sodium Conservation

Liddle's Syndrome

Liddle et al. (1963) described members of a family with hypertension, hypokalemic alkalosis, and negligible aldosterone secretion, apparently resulting from an unusual tendency of the kidneys to conserve sodium and excrete potassium even in the virtual absence of mineralocorticoids. Such patients have a mutation of the b or g subunits of the renal epithelial sodium channel, which causes increased sodium reabsorption in the distal nephron (Yamashita et al., 2001). By identifying the mutation in the family of index cases, some genetically affected adults have been found to have mild hypertension and minimal hypokalemia (Findling et al., 1997), raising the possibility that some patients with “primary” hypertension may have Liddle's syndrome (Alper, 2001). As is noted in Chapter 14, these clinical features are also seen in apparent mineralocorticoid excess caused by mutations in 11b-hydroxysteroid dehydrogenase, preventing conversion of cortisol to cortisone.

Activation of Mineralocorticoid Receptor

Geller et al. (2000) have identified a mutation in the mineralocorticoid receptor that causes early-onset hypertension that is markedly exacerbated in pregnancy. The exacerbation is a consequence of the altered receptor specificity, so that the high levels of progesterone and other steroids lacking 21-hydroxyl groups become potent agonists. It will soon become known whether this mutation is responsible for more instances of hypertension with low renin and low aldosterone.

Gordon's Syndrome

Another syndrome has been described with renal sodium and chloride retention that causes hypertension and suppression of the reninaldosterone mechanism, but with hyperkalemia due to impaired potassium excretion (Gordon, 1986). The syndrome, known as *pseudohypoaldosteronism type II* or Gordon's syndrome, is inherited as an autosomal dominant trait for which at least four loci have been recognized (Disse-Nicodème et al., 2000; Wilson et al., 2001). An elevated ARR has been noted, with aldosterone stimulated by hyperkalemia and renin suppressed by volume expansion (Stowasser, 2000).

Decreased Renal Sodium Conservation

No diagnostic confusion should occur with the two rare syndromes secondary to decreased sodium reabsorption wherein volume contraction leads to secondary hyperaldosteronism from increased renin secretion. Bartter's syndrome (Bartter et al., 1962) is usually recognized in early childhood and runs a severe clinical course with marked hypokalemia. Gitelman's syndrome (Gitelman et al., 1966) tends to appear later and run a milder course but is associated with a reduced quality of life (Cruz et al., 2001).

Iatrogenic Mineralocorticoid Excess

As with Cushing's syndrome, induced by exogenous glucocorticoids, aldosteronism may be induced by exogenous mineralocorticoids, even when absorbed through the skin in an ointment for the treatment of dermatitis (Lauzurica et al., 1988).

Conclusion

This long listing of various diseases, most involving hypokalemia and many with hypertension, should not imply the need for a long and complicated workup to diagnose primary aldosteronism. By following the flow diagram shown in Figure 13-5, one can usually make the correct diagnosis with relative ease.

During Pregnancy

Normal pregnancy is associated with elevated plasma aldosterone but also elevated renin activity. In 18 reported cases of primary aldosteronism diagnosed during pregnancy, usually presenting with marked hypokalemia, renin levels were reduced (Keely, 1998). Moreover, preexisting hypertension due to primary aldosteronism may be ameliorated during pregnancy, perhaps by antagonism of the effects of elevated aldosterone by the high progesterone levels (Murakami et al., 2000). Management is complicated by the inability to use most medical therapies, and laparoscopic adrenalectomy may be the preferred treatment.

Even more cases have been reported of pregnancy in women with GRA, 35 pregnancies in 16 patients (Wyckoff et al., 2000). Most of the pregnancies were successful, although hypertension often was exacerbated.

TYPES OF ADRENAL PATHOLOGY

Once the diagnosis of primary aldosteronism is made, the type of adrenal pathology must be ascertained, because the choice of therapy is different: surgical for an adenoma, medical for hyperplasia.

Aldosterone-Producing Adenomas

Solitary benign adenomas (Fig. 13-6) are almost always unilateral and most are small, weighing less than 6 g and measuring less than 3 cm in diameter. In various series, from 20% to 85% are smaller than 1 cm (Rossi et al., 2001). Histologically, most adenomas are composed of lipid-laden cells arranged in small acini or cords, similar in appearance and arrangement to the normal zona fasciculata, the middle zone of the adrenal cortex. Moreover, focal or diffuse hyperplasia, as seen in Figure 13-6, is usually present in both the remainder of the adrenal with the adenoma and the contralateral gland (Lack et al., 1990).

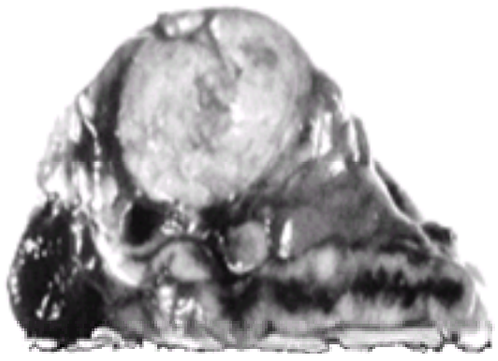

FIG. 13-6. Solitary 2.3-cm adrenal adenoma with diffuse hyperplasia removed from a patient with primary aldosteronism.

Gordon et al. (1995) postulate that such histologic hyperplasia outside the adenoma "suggests a genetic abnormality not limited to the adenoma cells." These investigators identified 57 patients among 23 families with two or more members who had adenomas that were not suppressed by glucocorticoids and that were biochemically and morphologically identical to nonfamilial primary aldosteronism (Stowasser and Gordon, 2000). However, in a subsequent review of the 730 patients diagnosed with primary aldosteronism in their unit, only five families were found with more than one member having the condition (Gordon et al., 2001). No genetic mutations have been recognized.

Thus, most patients with an adenoma do not have a family history or features that indicate a genetic basis for their condition (Pilon et al., 1999).

Because most of these benign adenomas are monoclonal in origin (Gicquel et al., 1994), their origin is more likely from proliferation of aldosterone-producing cells rather than from dysregulation of aldosterone synthesis, as may be seen in patients with bilateral hyperplasia (Mulatero et al., 2000).

Bilateral Adrenal Hyperplasia (Idiopathic Hyperaldosteronism)

In the early 1970s, reports of hyperaldosteronism without an adenoma but rather with bilateral adrenal hyperplasia began to appear (Baer et al., 1970; George et al., 1970). This is often referred to as *idiopathic hyperaldosteronism*. These patients tend to have milder biochemical and hormonal abnormalities that are less obvious than those seen with adenomas. The wide availability of hormonal assays and even wider availability of adrenal imaging techniques have made it much easier to recognize hyperplasia.

However, the better detail provided by newer imaging procedures may lead to confusion: Because the hyperplasia that often accompanies an adenoma can now be recognized, bilateral hyperplasia may be mistakenly diagnosed; because nodularity is often seen with hyperplasia, an adenoma may be mistakenly diagnosed (Glodny et al., 2000; Magill et al., 2001). Moreover, the clear separation between adenoma and hyperplasia may also be blurred by the recognition that, in response to suppression or stimulation tests, a solitary adenoma occasionally behaves like bilateral hyperplasia (Phillips et al., 2000; Tunny et al., 1991), and bilateral hyperplasia occasionally mimics the responses of a solitary adenoma (Biglieri, 1991). Therefore, anatomic evidence must be correlated with functional data to ensure the correct diagnosis (Magill et al., 2001; McAlister and Lewanczuk, 1998).

The presence of bilateral hyperplasia suggests a secondary response to some stimulatory mechanism rather than a primary neoplastic growth. Although claims have been made for novel aldosterone-stimulating substances in patients with bilateral hyperplasia (Komiya et al., 1991), none has been identified.

In view of the known polymorphism in the aldosterone synthase gene that is responsible for GRA (to be described shortly), such genetic polymorphisms have been sought in patients with bilateral hyperplasia that is not glucocorticoid-remediable. One group has found a variation in this gene in approximately half of 90 patients with bilateral hyperplasia (Mulatero et al., 2000), whereas another found increased aldosterone synthase activity and messenger RNA expression but no mutations in the gene in nine patients with bilateral hyperplasia (Takeda et al., 1999).

Unilateral Hyperplasia

Even more difficult to explain than the presence of bilateral hyperplasia are the 18 reported cases of hyperaldosteronism that apparently were caused by hyperplasia of only one adrenal gland (Morioka et al., 2000).

Glucocorticoid-Remediable Aldosteronism (Familial Hyperaldosteronism Type I)

Early Observations

In 1966, Sutherland and co-workers described a father and son with classic features of primary aldosteronism whose entire syndrome was completely relieved by dexamethasone, 0.5 mg four times a day (i.e., glucocorticoid-remediable). Subsequently, the syndrome was shown to follow an autosomal dominant mode of inheritance. In the early 1980s, Ulick et al. (1983) and Gomez-Sanchez et al. (1984) found increased levels of 18-hydroxylated cortisol in such patients. This led Ulick et al. (1990) to postulate that the syndrome was the result of the acquisition of aldosterone synthase activity, by cells of the zona fasciculata. This would explain the high levels of 18-hydroxylated steroids, which can be suppressed by exogenous glucocorticoid, which in turn suppresses ACTH, the normal stimulus to synthetic activity within the zona fasciculata.

Genetic Confirmation

The correctness of Ulick et al.'s (1990) postulate was proved in a striking manner by Lifton et al. (1992). Using restriction fragment– length polymorphism analysis of cells from eight affected members of a large kindred, these investigators found "complete linkage of glucocorticoid-remediable aldosteronism to a gene duplication arising from unequal crossing over, fusing the 5' regulatory region of 11-beta-hydroxylase to the 3' coding sequences of aldosterone synthase" (Lifton et al., 1992) (Fig. 13-7).

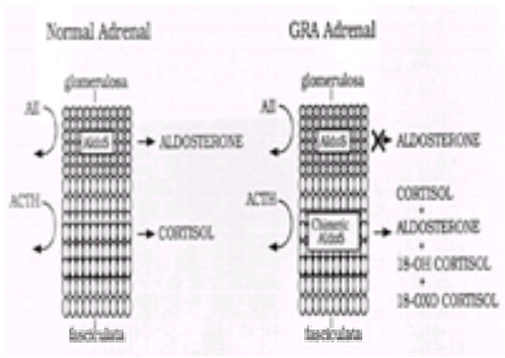

FIG. 13-7. Regulation of aldosterone production in the zona glomerulosa and cortisol production in the zona fasciculata in the normal adrenal, and model of the physiologic abnormalities in the adrenal cortex in glucocorticoid-remediable aldosteronism (GRA). Ectopic expression of aldosterone synthase enzymatic activity in the adrenal fasciculata results in GRA. 18-OH, 18-hydroxy; 18-OXO, 18-oxy; AII, angiotensin II; ACTH, adrenocorticotropic hormone; AldoS, aldosterone synthase. (Reprinted from Lifton RP, Dluhy RG, Powers M, et al. Hereditary hypertension caused by chimaeric gene duplications and ectopic expression of aldosterone synthase. *Nat Genet* 1992;2:66–74, with permission.)

The two genes lie next to one another on human chromosome 8 and are 94% identical, likely explaining the propensity to cross-over (Dluhy and Lifton, 1999).

Clinical and Laboratory Features

As more patients with GRA have been identified, variations in both genotype and phenotype have been identified. Different sites of gene cross-over do not seem to influence the phenotype, but patients who inherited GRA from their mothers have higher plasma aldosterone concentrations and BPs than those who inherited the chimeric gene from their fathers (Jamieson et al., 1995). Jamieson et al. (1995) conclude that “chronic exposure *in utero* to elevated plasma aldosterone concentrations may result in the permanent programming of mineralocorticoid-dependent blood pressure regulatory mechanisms, amplified in later life.”

In their review of this syndrome, Dluhy and Lifton (1999) noted that cases have been reported worldwide but not in blacks. The hyperaldosteronism is usually evident at birth, with inheritance as an autosomal dominant trait, occurring equally among men and women. The hypertension is often severe and poorly responsive to usual antihypertensive therapy, but some affected subjects in pedigrees are normotensive. An increased prevalence of strokes, particularly cerebral hemorrhage from intracranial aneurysm, has prompted the recommendation for magnetic resonance angiography beginning at puberty and every 5 years thereafter in all family members.

Dluhy and Lifton confirm the earlier observation that approximately half of affected patients are normokalemic, so that measurement of serum potassium is not a sensitive screening test. The absence of hypokalemia may be related to a number of factors, including a lesser mineralocorticoid activity of the 18-hydroxylated steroids, and to the inability of dietary potassium to stimulate aldosterone secretion when it arises from the zona fasciculata (Litchfield et al., 1997).

Diagnosis

Initially, the definitive diagnosis of GRA was based on dexamethasone suppression of aldosterone, but that has been shown to be unreliable (Fardella et al., 2001). Now that genetic testing is so easy, either by Southern blot or the faster and cheaper long polymerase chain reaction method, this is the preferred procedure. The genetic test can be obtained by contacting the International Registry for GRA: phone, 800-722-5520, extension 8404; or fax, 617-732-5764.

It is possible that variants of GRA are more common than now is recognized. In a preliminary report, Lim et al. (2000b) found an increased frequency of variations at the aldosterone synthase gene locus in 99 hypertensives with an elevated ARR whose condition was otherwise not defined. However, no GRA mutations were found in genetic testing of 300 randomly chosen hypertensives, so that the investigators recommended that screening should be targeted to those with a family history of early onset of hypertension associated with intracranial hemorrhage or a personal history of hypertension of early onset that is difficult to control or associated with hypokalemia (Gates et al., 2001).

Treatment

Suppressive doses of exogenous glucocorticoid will usually control the hypertension even if all the hormonal perturbations are not normalized (Stowasser et al., 2000). Spironolactone with or without a thiazide diuretic has been used without glucocorticoid suppression (Dluhy and Lifton, 1999).

Significance

Elucidation of this mutation represents the first description of a genetic basis of a form of hypertension in otherwise phenotypically normal humans (or animals). Beyond this rather limited population, polymorphic variability in the aldosterone synthase (CYP11B2) gene has been found in patients with “essential” hypertension by some investigators (Davies et al., 1999; Fardella et al., 1996; Pojoga et al., 1998) but not by others (Komiya et al., 2000; Schunkert et al., 1999). The search will go on, spurred by the old observations that adrenal suppression with dexamethasone will lower BP in some “essential” hypertensives (Hamilton et al., 1979).

In addition, as noted later in this chapter, almost all typical solitary adenomas secrete 18-hydroxylated steroids (Ulick et al., 1993). This pattern of secretion is similar, although to a much lesser degree, to that in GRA and is not seen in patients with bilateral adrenal hyperplasia. Despite the hormonal similarities between GRA and APAs, no mutations in the CYP11B1 (Pilon et al., 1999) or CYP11B2 (Carroll et al., 1996) gene has been found in the adenomas.

Other Pathologies

Carcinoma

Aldosterone-producing carcinomas are rare, with only 28 having been reported (Dixon and Bing, 2001). Most are associated with concomitant hypersecretion of other adrenal hormones, but a few may hypersecrete only aldosterone (Touitou et al., 1992). Even small adrenal carcinomas may cause florid hyperaldosteronism (Rossi et al., 2000).

Associated Conditions

Patients have been reported with primary aldosteronism caused by an adrenal adenoma in association with acromegaly (Dluhy and Williams, 1969), primary hyperparathyroidism, the multiple endocrine neoplasia 1 syndrome (Gordon et al., 1995), neurofibromatosis (Biagi et al., 1999), and familial adenomatous polyposis (Alexander et al., 2000). An APA may coexist with a non-functioning contralateral adrenal tumor (Hollak et al., 1991). In one patient, hyperaldosteronism has been found in association with non-Hodgkin's lymphoma (Mulatero et al., 2001).

Extraadrenal Tumors

Single ectopic aldosterone-producing tumors have been found in the kidney (Abdelhamid et al., 1996) and ovary (Kulkarni et al., 1990).

DETERMINING THE TYPE OF ADRENAL PATHOLOGY

Various procedures are available for determining the type of adrenal pathology (Table 13-5). This list is much shorter than in previous editions of this book because of the ascendancy of AVS when any ambiguity is noted on CT imaging or MRI. Some investigators recommend AVS even when there is no apparent ambiguity because

of the vagaries of adrenal pathology (Magill et al., 2001; Phillips et al., 2000). At the Mayo Clinic, AVS is performed in all patients with confirmed primary aldosteronism who do not have a solitary adrenal mass measuring at least 1 cm on imaging (Sawka et al., 2001).

Technique	Adenoma	Hyperplasia	Discriminatory value
Basal plasma 18-OH-B	>65 ng/dL	<65 ng/dL	Good
Basal 18-oxo-F, 18-OHF	Increased	Normal[a]	Good
Upright posture (rise in PA)	<30%	>30%	Fair
Adrenal computed tomography and magnetic resonance imaging	Unilateral mass	Bilaterally enlarged	Good
Adrenal venous aldosterone-cortisol ratio	Increased on side of adenoma	Equal	Excellent
Adrenal scintiscan with [^{75}I]cholesterol + dex	Unilateral persistent uptake	Bilateral suppressed uptake	Excellent

dex, dexamethasone; 18-oxo-F, 18-oxycortisol; 18-OH-B, 18-hydroxycorticosterone; 18-OHF, 18-hydroxycortisol; PA, plasma aldosterone.
[a]Markedly elevated in glucocorticoid-remediable aldosteronism.

TABLE 13-5. *Techniques to differentiate adrenal adenoma from bilateral hyperplasia*

Ancillary Procedures

In general, autonomous lesions that can be cured by surgery (adenomas and the rare primary adrenal hyperplasia) display their autonomy from the normal control of aldosterone production by the renin-angiotensin mechanism by having (a) high levels of aldosterone and its precursor, 18-OH-corticosterone, along with more severe clinical features of aldosteronism; (b) little or no response to stimulation of renin-angiotensin, such as during an upright posture test; and (c) the production of hybrid steroids such as 18-OH-cortisol.

Aldosterone and Renin Levels

Although adenomas tend to be associated with higher BP and aldosterone levels but lower renin and potassium levels than hyperplasia, these alone cannot make the differentiation.

Other Adrenal Steroids

Most adenomas, but not hyperplastic glands, secrete excess amounts of both normal precursors (e.g., 18-OH-B), and hybrid steroids [e.g., oxo-F (18-oxo-F, 18-OHF)] (Ulick et al., 1993). In this series, urine 18-oxo-F levels exceeded 16 µg per day in 19 of 21 patients with an adenoma and were less than 16 µg per day in all 20 patients with bilateral hyperplasia. The level of serum 18-OH-B that provides the best separation appears to be approximately 65 ng per dL (Phillips et al., 2000), some-what lower than the originally recommended 100 ng per dL (Kater et al., 1989).

Response to Upright Posture

This test depends on changes in plasma aldosterone in response to variations in endogenous stimuli during 2 to 4 hours of upright posture (Ganguly et al., 1973). The premise is that adenomas are not responsive to postural increases in angiotensin (which stay suppressed anyway) but are exquisitely sensitive to the diurnal fall in plasma ACTH, whereas hyperplasia is responsive to even small postural rises in angiotensin. Thus, patients with hyperplasia should have an even greater than normal *rise* in plasma aldosterone after 4 hours of standing, whereas patients with an adenoma show an anomalous *fall* in plasma aldosterone, in parallel with the falling plasma ACTH levels during the early morning hours.

By subtracting the percentage of cortisol change from the percentage of aldosterone change, Fontes et al. (1991) found that a corrected aldosterone increase of less than 30% identified 76 of 89 adenomas, but such a blunted rise was present in 11 of 57 hyperplasias. Others find that a fall in plasma aldosterone or 18-OH-B levels is helpful in diagnosing an adenoma, but most adenomas are associated with as much of a rise in steroid levels as are hyperplasias (Phillips et al., 2000).

Localizing Techniques

The greater accuracy provided by CT, MRI, scintigraphy, and AVS has diminished the need for the previously described ancillary procedures.

Adrenal Computed Tomography or Magnetic Resonance Imaging

Most APAs are visible by CT or MRI scans even though they may be less than 1 cm in size (Fig. 13-8). MRI with chemical shift imaging may be useful in distinguishing an adrenal incidentaloma from a functioning adenoma, which typically has a higher lipid content (Sohaib et al., 2000).

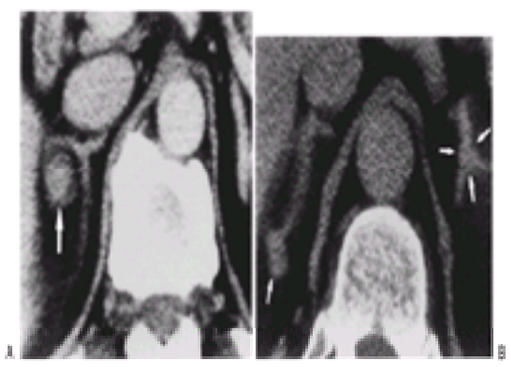

FIG. 13-8. Computed tomographic scans of two patients with clinical features of primary aldosteronism. **A:** A 1.5-cm solitary adenoma (*arrow*) in the right adrenal. The diagnosis of aldosteronoma was confirmed with relief of the syndrome by resection of the gland. **B:** Several 9-mm nodules (*arrows*) in both adrenal glands, which are hyperplastic. The patient's hypokalemia and hypertension were controlled medically. (Reprinted from Radin DR, Manoogian C, Nadler JL. Diagnosis of primary hyperaldosteronism: importance of correlating CT findings with endocrinologic studies. *AJR Am J Roentgenol* 1992;158:553–557, with permission.)

Increasingly, however, the clinical issue is not in making the diagnosis of a functioning lesion, as the multiple procedures described in the previous pages can do so with virtual certainty. The issue is differentiating a small solitary adenoma from bilateral (often nodular) hyperplasia, a problem that has grown progressively with the improved resolution of CT and MRI scans, which are now capable of identifying small nodules that are often seen coexisting with a solitary functioning adenoma (Doppman, 1997; (Harper et al., 1999; McAlister and Lewanczuk, 1998; Young, 1997).

In all four of these series, including a total of 181 patients with hyperaldosteronism, a significant number of what turned out to be solitary adenomas were thought to be bilateral hyperplasia on CT scan, and a significant number of bilateral hyperplasias by CT turned out to be adenomas. In the 55 patients reported by Doppman (1997), of the 28 lesions that looked like hyperplasia on CT, 18 were found to be a solitary adenoma. Similarly discordant results of CT or MRI with surgical findings have led to an increasing consensus that AVS be done either on all patients with proved aldosteronism (Glodny et al., 2000; Magill et al., 2001) or at least on those

without a solitary adenoma measuring 1 cm or larger (Sawka et al., 2001).

Adrenal Venous Sampling

Definitive guidelines on the performance and interpretation of AVS have been provided by Rossi et al. (2001), who reported their findings in 104 patients with primary aldosteronism and equivocal CT or MRI findings, as defined by the absence of a solitary adrenal mass larger than 18 mm. AVS was feasible in 97.1% of attempts and, in 80.6% of cases, bilateral samples were obtained almost simultaneously. Without ACTH stimulation, they found that the greatest selectivity in ensuring AVS accuracy was a plasma cortisol in the adrenal venous sample 1.1 or more times higher than in the inferior vena caval sample. With bilateral selective AVS, a ratio of aldosterone/cortisol of one side over the contralateral side of 2.0 or greater identified a unilateral source of excess aldosterone in 80% of the patients. Rossi et al. (2001) also noted that unilateral sampling of the left adrenal vein (which is easier to catheterize than the right) was of no value in identifying the type of pathology.

These data are encouraging in one sense, because good discrimination was provided by AVS in most patients, despite ambiguous findings on CT or MRI. Presumably even better results would be found in those with well-defined solitary adenomas or bilateral hyperplasia. On the other hand, even in the hands of such experienced investigators, 20% of patients could not be correctly characterized by AVS.

All who perform AVS or who wish to interpret data from the procedure should read the report of Rossi et al. (2001) and the previous review by Doppman and Gill (1996).

Adrenal Scintigraphy

Adrenal scintiscans with the isotope 6-b-[^{131}I]-iodomethyl-19-norcholesterol (NP-59) offer discrimination almost as good as that found by AVS but with less discomfort. Results are better with suppression scintiscans using 0.5 or 1.0 mg dexamethasone every 6 hours to discriminate between adenomas, which remain visible, and bilateral hyperplasia, which fades after a few days of dexamethasone (Shapiro et al., 1994).

Although small adenomas with relatively low uptake of the tracer may give false-negative results (Nomura et al., 1990) and spironolactone may increase bilateral uptake (Shapiro et al., 1994), the published experiences with adrenal scintiscans have shown discrimination between adenoma and hyperplasia in 90% of cases (Francis et al., 1992).

Overall Plan

As seen in Figure 13-5, once the presence of primary aldosteronism has been confirmed, a CT or MRI scan of the adrenals should be obtained. If a solitary adrenal mass larger than 1 cm is seen, unilateral adrenalectomy should be recommended. If two symmetrically enlarged glands are seen, a posture study and a serum 18-OH-B assay should be done. If they are indicative of bilateral hyperplasia, medical therapy should be recommended.

If the data do not correlate with the CT and MRI findings or if an adrenal mass smaller than 1 cm is present, AVS should be performed, preferably in a center that has considerable experience with the procedure. If the results remain equivocal, the patient should be treated medically and the evaluation repeated in 6 to 12 months.

Remember that young patients and particularly those with a family history of aldosteronism should be evaluated for GRA, as described earlier in this chapter. The problem of excluding adrenal hyperfunction in adrenal glands found incidentally to have a mass by abdominal CT done for other reasons is addressed in the first portion of Chapter 12.

THERAPY

Once the type of adrenal pathology has been ascertained, surgery should be done if the diagnosis is *adenoma*, and medical therapy is indicated if the diagnosis is *bilateral hyperplasia*. Although there are reports of relief of aldosteronism by removal of a unilaterally hyperplastic gland or one of two hyperplastic glands (Irony et al., 1990), surgery should be performed only if an adrenal adenoma is larger than 1 cm as visualized by scan or scintigraphy or if AVS clearly defines a unilateral source of the aldosterone hypersecretion.

Surgical Treatment

Preoperative Management

Once the diagnosis of adenoma is made, a 3- to 5-week course of spironolactone therapy may be given to normalize the various disturbances of electrolyte composition and fluid volume, easing anesthetic, surgical, and postoperative management.

Surgical Technique

With improved preoperative diagnosis of an adenoma, laparoscopic adrenalectomy has become the procedure of choice (Gasman et al., 1998) even in very obese patients (Fazeli-Matin et al., 1999) and can be done as an outpatient procedure (Gill et al., 2001).

If bilateral hyperplasia is found at surgery despite the preoperative diagnosis of an adenoma, only a unilateral adrenalectomy should be done. In view of the poor overall results with bilateral adrenalectomy and its complications, one gland should be left intact.

Postoperative Complications

Hypoaldosteronism

The patient, even if given spironolactone preoperatively, may develop hypoaldosteronism, with an inability to conserve sodium and excrete potassium. This may persist for some time after renin levels return to normal, analogous to the slowness of the return of cortisol production after prolonged ACTH suppression by exogenous glucocorticoids.

The aldosterone deficiency is usually not severe or prolonged and can be handled simply by providing adequate salt, without the need for exogenous glucocorticoid or mineralocorticoid therapy. However, 5 of 37 patients who underwent unilateral adrenalectomy for an adenoma were symptomatically hypotensive 1 year later, some with low plasma cortisol, others with low plasma aldosterone and epinephrine levels (Gordon et al., 1989).

Sustained Hypertension

The hypertension may persist for some time; a few patients require years for return of normal BP. In 13 series published after 1978, 64% of 466 patients were cured of hypertension, and 33% were improved (Shenker, 1989). In a series of 97 adrenalectomies, 57 of which were laparoscopic, performed at the Mayo Clinic from 1993 to 1999 for primary aldosteronism, hypertension was improved in 95% and cured in 32% (Sawka et al., 2001). Cure was independently predicted by a negative family history of hypertension, relatively mild preoperative hypertension, and a very high preoperative ARR.

If the BP fails to respond, hyperfunctioning adrenal tissue may have been left. More likely is the presence of coincidental primary hypertension, as would be expected in at least 20% of cases, or the occurrence of significant renal damage from the prolonged secondary hypertension (Proye et al., 1998). Few patients with bilateral hyperplasia respond to unilateral (Groth et al., 1985) or even to bilateral adrenalectomy (Ferriss et al., 1978b).

Medical Treatment

Chronic medical therapy with spironolactone or, if that is not tolerated, amiloride with or without a thiazide diuretic is the treatment of choice for patients with

hyperplasia, patients with an adenoma who are unable or unwilling to have surgery, patients who remain hypertensive after surgery, and patients with equivocal findings (Ghose et al., 1999; Lim et al., 2001).

Spironolactone usually lowers the BP and keeps it down (Ferriss et al., 1978a). Doses of 100 to 200 mg per day may be needed initially, but a satisfactory response may then be maintained with as little as 50 mg per day. The combination of spironolactone with a thiazide diuretic may provide even better control and allow for smaller doses of spironolactone. With these lower doses, the various side effects are generally minor, and in only 3 of 95 cases were they severe enough to lead to withdrawal of the drug (Ferriss et al., 1978a). In the near future, a more selective aldosterone receptor antagonist, eplerenone, will be available, providing benefits equal to but fewer side effects than spironolactone (Funder, 2000). If additional antihypertensive therapy is needed, calcium blockers or angiotensin-converting enzyme inhibitors may be used (Lim et al., 2001).

In patients with adrenal cancer, various inhibitors of steroidogenesis are useful. These are described in Chapter 14 in the section devoted to treatment of Cushing's syndrome.

CONCLUSION

Primary aldosteronism remains a fascinating disease that may be more common than was previously thought but less common than some now claim. On the other hand, a number of other causes of hypertension with clinical features of mineralocorticoid excess have been identified, as covered in the next chapter.

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*Conversion of laboratory values from traditional units to SI units can be performed as follows: *Plasma aldosterone*, from nanograms per deciliter to picomoles per liter: multiply by 27.7; *Urine aldosterone*, from micrograms per day to nanomoles per day: multiply by 2.77; *PRA*, from nanograms per milliliter per hour to nanograms per liter: multiply by 0.278.

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14
Hypertension Induced by Cortisol or Deoxycorticosterone

The preceding chapter described the syndromes of hypertension induced by primary aldosterone excess. This chapter covers syndromes in which hypertension is induced by other adrenal steroids: *cortisol*, either in excess (Cushing's syndrome) or with increased binding to mineralocorticoid receptors (apparent mineralocorticoid excess and licorice ingestion); or *deoxycorticosterone* (DOC; congenital adrenal hyperplasias).

CUSHING'S SYNDROME

Significance

Cushing's syndrome is a serious disease. Hypertension is present in more than 80% of patients with Cushing's syndrome, is often difficult to treat (Fallo et al., 1993), and contributes to a mortality rate, even after successful therapy, that is almost four times that of an age-and gender-matched population (Lindholm et al., 2001).

Pathophysiology

Cushing's syndrome is caused either by excess endogenous cortisol in the idiopathic form or excess exogenous steroids in the iatrogenic form. The idiopathic disease may be either dependent on or independent of adrenocorticotropic hormone (ACTH) (Table 14-1; Fig. 14-1). The most common type, termed *Cushing's disease*, is due to overproduction of ACTH from a pituitary microadenoma, with resultant diffuse bilateral adrenal hyperplasia. Ectopic ACTH production may come from multiple types of tumors, the largest number being malignant small-cell carcinomas of the lung (Boscaro et al., 2001).

	No. of affected patients per study		
	Orth, 1995	Newell-Price et al., 1998	Boscaro et al., 2000
Total no. of patients	630	306	302
ACTH-dependent			
Pituitary ACTH (Cushing's disease)	68	68	66
Ectopic ACTH syndrome	12	10	7
Ectopic CRH syndrome	<1	5	<1
Macronodular adrenal hyperplasia	—	—	2
ACTH-independent			
Adrenal adenoma	10	9	16
Adrenal carcinoma	8	7	6
Micronodular hyperplasia	1	2	<1
Adrenal hyperplasia from other stimuli (e.g., gastric inhibitory polypeptide)	<1	—	<1

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

TABLE 14-1. *Prevalence of various types of Cushing's syndrome in three separate series (in percentages)*

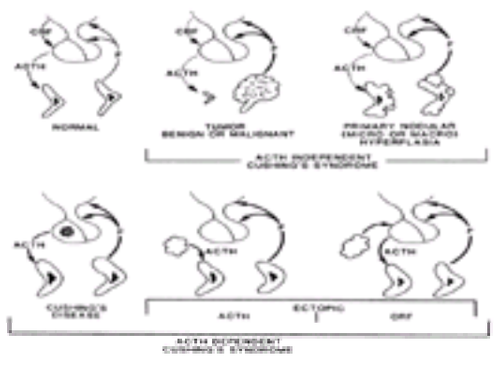

FIG. 14-1. Causes of endogenous Cushing's syndrome. The lesions of the top arise within the adrenal. Those in the bottom arise within the pituitary (Cushing's disease) or from ectopic production of adrenocorticotropic hormone or corticotropin-releasing factor (CRF). ACTH, adrenocorticotropic hormone; F, cortisol. (Reprinted from Carpenter PC. Diagnostic evaluation of Cushing's syndrome. *Endocrinol Metab Clin North Am* 1988;17:445–472, with permission.)

ACTH-independent forms are motly benign adrenal adenomas or malignant carcinomas, but various forms of hyperplasia may pose diagnostic difficulty.

As noted in Chapter 12, the number of adrenal tumors found incidentally by abdominal computed tomography (CT) or magnetic resonance imaging (MRI) is increasing. As many as 20% of these so-called incidentalomas secrete cortisol in a partially unregulated manner, often in association with hypertension, diabetes, and generalized obesity (Rossi et al., 2000).

A number of interesting variants have been reported, including

- Spontaneously remitting disease (Ishibashi et al., 1993).
- Cyclic or periodic disease (Walker et al., 1997).
- Association with overt hypothalamic disorders (Stewart et al., 1992).
- Transition from pituitary-dependent to pituitary-independent disease (Hermus et al., 1988).
- ACTH-independent bilateral macronodular hyperplasia, which is often massive (Doppman et al., 2000), may be familial (Lieberman et al., 1994), and may be

associated with the expression of ectopic receptors for various hormones, including the gastric inhibitory polypeptide, vasopressin, b-adrenergic agonists, luteinizing hormone or human chorionic gonadotropin, or serotonin (Lacroix et al., 2001). Such receptors are occasionally found in adrenal adenomas as well.
- Pigmented micronodular dysplasia (Samuels and Loriaux, 1994), in most cases as part of the autosomal dominant familial syndrome with cardiac and skin myxomas, the Carney complex (Malchoff, 2000).
- Association with pheochromocytoma (Amos and McRoberts, 1998), chemodectoma, and carcinoid tumors (Tremble et al., 2000).
- Increased sensitivity of peripheral glucocorticoid receptors causing clinical features without increased levels of cortisol (Boscaro et al., 2000).

Hypertension with Glucocorticoid Excess

Clinical Features

Hypertension is present in approximately 80% of patients with Cushing's syndrome. It may be severe; in the series of Ross and Linch (1982), 10 of 70 patients had blood pressure (BP) exceeding 200/120 mm Hg, and all but one of these patients died, despite treatment of the Cushing's syndrome. Among all 70 patients, 55% had an abnormal electrocardiogram and 28% had cardiomegaly. The severity of the hypertension may be related to the abolition of the normal nocturnal fall in BP seen after exogenous glucocorticoid administration and in patients with Cushing's syndrome (Imai et al., 1988). The longer the duration of hypertension, the greater is the likelihood that it will persist after relief of the syndrome (Suzuki et al., 2000).

Hypertension is relatively rare in patients who take exogenous glucocorticoids (Sato et al., 1995), because of the use of steroid derivatives with less mineralocorticoid activity than cortisol. However, significant rises of BP can occur within 5 days of the administration of cortisol in fairly high doses (Whitworth et al., 2000).

Mechanisms of Hypertension

Multiple mechanisms may be responsible for the hypertension so common in Cushing's syndrome (Whitworth et al., 2000). The mechanisms may include

- A sodium-retaining action of the high levels of *cortisol*, through binding to either mineralocorticoid receptors (Ulick, 1996) or nonreceptor mechanisms (Montrella-Waybill et al., 1991). Although cortisol is 300 times less potent a mineralocorticoid than is aldosterone, 200 times more cortisol is normally secreted; and this level is increased by 2 times or more in Cushing's syndrome. When the mineralocorti coid antagonist spironolactone was given along with cortisol, however, all of the mineralocorti coid effects (weight gain, potassium wastage) were blunted, but the BP still rose, suggesting that mineralocorticoid effects are not totally responsible for cortisol-induced hypertension (Whitworth et al., 2000).
- Increased production of *mineralocorticoids*. Although usually noted only in patients with adrenal tumors, increased levels of 19-nor-deoxycorticosterone (Ehlers et al., 1987), DOC and, less commonly, aldosterone (Cassar et al., 1980) have been found in patients with all forms of the syndrome.
- Reduced activity of various vasodepressor mechanisms (Saruta, 1996), in particular endothelial nitric oxide (Mangos et al., 2000).
- Increased levels of *renin* substrate and an increased responsiveness to various *pressors* (Pirpiris et al., 1992), likely by effects on vascular receptors which may, in turn, be mediated by an overwhelming of the 11-b-hydroxy-steroid dehydrogenase capacity to convert cortisol to cortisone in vascular tissue (Brem, 2001). In those with ACTH-dependent disease, cortisol effects on endothelial cells may be potentiated (Hatakeyama et al., 2000).

Other mechanisms may also be involved, including an increase in erythropoietin (Whitworth et al., 2000).

Clinical Features

Many more patients with cushingoid features are seen than the relatively few who have Cushing's syndrome. The syndrome is more likely in patients with the clinical features shown in Table 14-2 (Boscaro et al., 2001; Danese and Aron, 1994). In addition, significant hypokalemia is usually noted with the ectopic ACTH syndrome.

Clinical features	Approximate incidence (%)
General	
Obesity	80–95
Truncal*	45–95
Hypertension	70–90
Headache	10–50
Skin	
Facial plethora	70–90
Hirsutism	70–80
Purple striae*	50–70
Bruising*	30–70
Neuropsychiatric	60–95
Gonadal dysfunction	
Menstrual disorders	75–95
Impotence or decreased libido	65–95
Musculoskeletal	
Osteopenia	75–85
Weakness from myopathy*	30–90
Metabolic	
Glucose intolerance, diabetes	40–90
Kidney stones	15–20

*Most discriminatory features.
Modified from Danese RD, Aron DC. Cushing's syndrome and hypertension. Endocrinol Metab Clin North Am 1994;23:299–324.

TABLE 14-2. *Clinical features of Cushing's syndrome*

Cushing's syndrome in children is usually manifested by weight gain and growth retardation, with systolic hypertension noted in 93% of 63 young patients (Magiakou et al., 1997). Fortunately, such children usually become normotensive within a few months of surgical cure, and they are able to catch up in their linear growth (Lebrethon et al., 2000).

Differential Diagnosis

Patients with endogenous *depression* without Cushing's syndrome may have poorly suppressible hypercortisolism related to increased ACTH pulse frequency (Mortola et al., 1987), but their basal cortisol levels are usually normal and they do not hyperrespond to corticotropin-releasing hormone (CRH) (Gold et al., 1986). Moreover, depressed patients usually have a normal rise in cortisol during an insulin tolerance test and a normal suppression after the opiate agonist loperamide, unlike most patients with Cushing's syndrome (Newell-Price et al., 1998).

Alcoholics often display numerous features suggestive of Cushing's syndrome, including hypertension and a failure to suppress plasma cortisol after overnight dexamethasone (Stewart et al., 1993), which likely reflects increased secretion of corticotropin-releasing factor (Groote Veldman and Meinders, 1996). Alcohol should not be consumed for at least 1 week before studies are done.

Pregnant women often have features suggestive of Cushing's syndrome; the rare appearance of Cushing's syndrome during pregnancy may pose diagnostic dilemmas (Keely, 1998).

Laboratory Diagnosis

Two somewhat contradictory scenarios exist in relation to the diagnosis of Cushing's syndrome. First, the disease is being looked for in more patients with suggestive clinical features, such as poorly controlled obese diabetics; in one study, 4% were found to have Cushing's syndrome (Leibowitz et al., 1996). This scenario requires screening tests with high specificity (i.e., few false-positive results) so that fewer suspects will be put through extensive confirmatory testing.

The second scenario relates to the usually long duration between onset of symptoms and the time of diagnosis, averaging 29 months in a multicenter study from Italy (Invitti et al., 1999). This scenario requires confirmatory tests with high sensitivity (i.e., few false-negative results) so that all patients can be correctly identified as early as possible. In view of the serious nature and the often irreversibility of the complications of the disease, the best balance is likely to be with a number of tests done over a short interval to achieve maximal predictive power.

Screening Tests

The extent of the workup of patients suspected of having Cushing's syndrome varies with the clinical situation. An overnight 1-mg dexamethasone suppression test will be adequate for most patients who have only minimally suggestive features; patients with highly suggestive features should have the low-dose urinary dexamethasone suppression test, 24-hour urinary free cortisol test and, if feasible, a sleeping mid-night plasma cortisol test (Boscaro et al., 2001; Newell-Price et al., 1998) (Fig. 14-2).

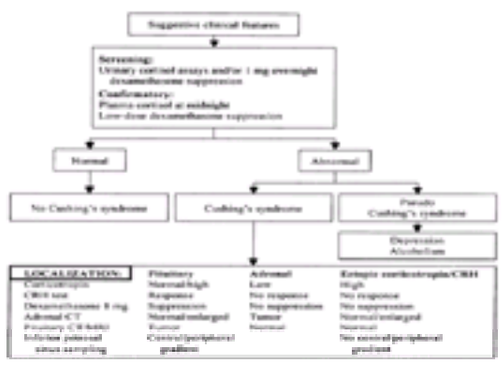

FIG. 14-2. An approach to the differential diagnosis of Cushing's syndrome. CRH, corticotropinreleasing hormone; CT, computed tomography; MRI, magnetic resonance imaging.

Urinary Cortisol

The diagnostic accuracy of urine assays may be enhanced by high-performance liquid chromatography, which determines both cortisol and cortisone, particularly to rule out Cushing's syndrome from exogenous sources (Lin et al., 1997). Urinary free cortisol can be measured in an overnight (8 p.m. to 8 a.m.) specimen and expressed as a ratio to urine creatinine, providing sensitivity and specificity equal to that of a 24-hour specimen (Corcuff et al., 1998).

Overnight Plasma Suppression

For screening, the suppression test that uses a single bedtime 1-mg dexamethasone dose, after which the plasma cortisol is measured at 8 a.m. the next day, has worked well, with a sensitivity greater than 98% (Boscaro et al., 2001). A level of less than 5 µg per dL indicates normal suppression, but most normal levels are less than 2 µg per dL (Danese and Aron, 1994). False-positive results are seen in approximately 10% of non-Cushing's patients. One reason is too-rapid inactivation of the exogenous dexamethasone to suppress ACTH by drugs that stimulate the hepatic drug-metabolizing enzymes, such as diphenylhydantoin, barbiturates, tolbutamide, rifampin, and perhaps alcohol (Trainer and Grossman, 1991). Another reason may be the overriding effect of stress or endogenous depression (Danese and Aron, 1994).

Confirmatory Tests

Low-Dose Dexamethasone Suppression

If the overnight screening test is abnormal or the clinical evidence is strong, the presence of hypercortisolism can be virtually ensured by the finding that plasma or urinary levels of cortisol cannot be normally suppressed by a low dose of 0.5 mg dexamethasone every 6 hours for 2 days (Liddle, 1960). This amount of dexamethasone is equivalent to nearly 40 mg cortisol, approximately twice the normal daily secretion rate. Cortisol hypersecretion is confirmed if plasma cortisol exceeds 5 µg per dL 6 hours after the last of the eight doses or urinary cortisol is higher than 10 µg per day or urinary 17-hydroxy-corticoid is more than 2.5 mg per day (Orth, 1995). If levels of 20 µg per day or 3.5 mg per day, respectively, are used, the sensitivity was found to be 93% in a series of 426 patients with Cushing's syndrome (Invitti et al., 1999).

Dexamethasone suppression tests may give anomalous results because hormone hypersecretion may be cyclic or variable. Pseudo-Cushing's states, including depression, may be more accurately excluded by adding a CRH stimulation test 2 hours after completion of the low-dose dexamethasone test (Yanovski et al., 1998).

Desmopressin Stimulation

In addition, the response of plasma cortisol and ACTH to desmopressin (a vasopressin analog), 10 µg as an intravenous bolus, gave 94% accuracy in distinguishing 76 patients with Cushing's syndrome from 30 with pseudo-Cushing's states, results that were better than those seen with the previously described screening tests (Moro et al., 2000).

Establishing the Cause of Cushing's Syndrome

Once Cushing's syndrome has been diagnosed, the anatomic cause needs to be determined accurately to guide therapy (Fig. 14-2).

Corticotropin (Adrenocorticotropic Hormone) Assay

As Boscaro et al. (2001) note:

> Corticotropin measurement represents the first step and the best way to distinguish corticotropindependent from corticotropinindependent hypercortisolism. Concentrations below the limit of detection at 0900 h indicate autonomous adrenal hyperfunction. The higher the plasma corticotropin concentration, the more likely is an ectopic source of the hormone, particularly a small-cell lung carcinoma. In active Cushing's disease, plasma corticotropin at 0900 h may be within the normal range, and there may be a significant over-lap between concentrations seen with pituitary adenomas and “occult” ectopic corticotropinsecreting tumours.

High-Dose Dexamethasone Suppression

Using new criteria of suppression of urinary free cortisol to less than 10% of baseline for the diagnosis of pituitary-dependent Cushing's disease, the high-dose (2 mg four times daily) dexamethasone suppression test provides 70% sensitivity and 100% specificity (Boscaro et al., 2001). These investigators find this test, together with CRH stimulation, to be most useful in distinguishing pituitary from ectopic ACTH-dependent Cushing's syndrome.

Imaging Techniques

CT or MRI scans of the adrenal and pituitary are often diagnostic but, as NewellPrice and Grossman (1999) note:

> Non-invasive tests are far from perfect. The situation is made worse by the fact that pituitary corticotroph adenomas are commonly only a few millimetres in diameter, and may not be visualized even with modern MRI in up to 40% of cases, a finding replicated in the Italian series (Invitti et al., 1999). To complicate matters further, pituitary “incidentalomas” are present in 10% of the appropriate age-group on MRI (Hall et al., 1994).

Inferior Petrosal Sinus Sampling

Bilateral sampling of the inferior petrosal sinuses is a powerful means of confirming whether or not the source of corticotropin is the pituitary, especially if imaging is

negative. Boscaro et al. (2001) report that a ratio of central to peripheral ACTH of greater than 2 after CRH stimulation provides a sensitivity of 95% to 97% and a specificity of 100% in diagnosing pituitary-dependent Cushing's disease. As they note, “The test requires experienced teams in specialized centres and should be reserved only for patients in whom diagnostic doubts persist after the more common testing” (Boscaro et al., 2001).

If data point to an ectopic ACTH-secreting tumor, conventional radiology and ^{111}In-pentreotide scintigraphy are used to locate the tumor (de Herder and Lamberts, 1999).

In view of all the vagaries that often confuse the differential diagnosis of the etiology of Cushing's syndrome (Boscaro et al., 2000), referral to a medical facility with experience in dealing with such patients is almost always appropriate.

Treatment

Treatment of the Hypertension

Until definitive therapy is provided, the hypertension that accompanies Cushing's syndrome can be treated with the antihypertensive agents described in Chapter 7. Because excess fluid volume is involved, a diuretic, in combination with the aldosterone antagonist spironolactone, is an appropriate initial choice. After definitive therapy, hypertension usually improves, but atherosclerotic risk factors often persist, likely because of residual abdominal obesity and insulin resistance (Colao et al., 1999).

Treatment of the Syndrome in General

The choice of definitive therapy depends on the cause of the syndrome; many choices are available (Table 14-3).

Class	Site	Therapy
Surgery	Pituitary	Transsphenoidal microsection; transfrontal hypophysectomy
	Adrenal	Unilateral adrenalectomy; bilateral adrenalectomy
Radiation	External	High-voltage x-ray (cobalt) with or without minitorte (etc.), α-particle, proton beam (cyclotron)
	Internal	Implants of yttrium 90, gold 198
Drugs	Acting at hypothalamo-pituitary level	Serotonin antagonists (cyproheptadine, metergoline, ketanserin, ritanserin)
		Dopamine agonists (bromocriptine, lisuride)
		Gamma-aminobutyric acid agonists (sodium valproate)
		Somatostatin analogs (octreotide)
	Acting on adrenocortical steroid synthesis	Mitotane
		Metyrapone
		Aminoglutethimide
		Ketoconazole
		Etomidate
		Trilostane
	Acting on receptors	Glucocorticoid antagonists (mifepristone)

TABLE 14-3. *Therapies for Cushing's syndrome*

- Benign adrenal tumors should be surgically removed, increasingly by laparoscopy (Acosta et al., 1999).
- For adrenal cancers and ectopic ACTH tumors that cannot be resected, removal of the adrenal may be helpful, but chemotherapy is usually needed (Chou and Lin, 2000; Miller and Crapo, 1993).
- For pituitary tumors, transsphenoidal microsurgical removal of pituitary tumors has become the treatment of choice (Groote Veldman et al., 2000). Unilateral adrenalectomy followed by external pituitary irradiation has been successful (Nagesser et al., 2000).
- The drugs listed in Table 14-3 are mainly used to overcome severe complications quickly, either in preparation for surgery or whenever definitive treatment must be delayed.
- Mifepristone has been used for long-term treatment (Chu et al., 2001) and, in experimental models, retinoic acid has been effective (Páez-Pereda et al., 2001).

SYNDROMES WITH INCREASED ACCESS OF CORTISOL TO MINERALOCORTICOID RECEPTORS

Less common than Cushing's syndrome caused by cortisol excess are a variety of fascinating syndromes wherein normal or increased levels of cortisol exert a mineralocorticoid effect by binding to the renal mineralocorticoid receptors. As noted in Chapter 13 and depicted in Figure 14-3, the normal renal mineralocorticoid receptor is as receptive to glucocorticoids as it is to mineralocorticoids. The 11b-hydroxysteroid dehydrogenase type 2 isoform (11b-HSD2) enzyme in the renal tubules upstream to these receptors normally converts the large amounts of fully active cortisol to the inactive cortisone, thereby leaving the mineralocorticoid receptors open to the effects of aldosterone (Cooper and Stewart, 1998).

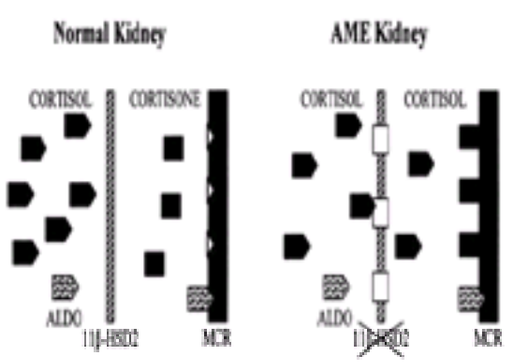

FIG. 14-3. Enzyme-mediated receptor protection. Normally, 11b-hydroxysteroid dehydrogenase type 2 (11b-HSD2) converts cortisol to inactive cortisone in the more proximal nephron, protecting mineralocorticoid receptors (MCR) from cortisol and allowing selective access for aldosterone. When 11b-HSD2 is defective (e.g., in congenital deficiency [apparent mineralocorticoid excess (AME)] or after licorice administration), cortisol gains inappropriate access to mineralocorticoid receptors, resulting in sodium retention and potassium wasting. ALDO, aldosterone. (Modified from Cerame BI, New MI. Hormonal hypertension in children: 11b-hydroxylase deficiency and apparent mineralocorticoid excess. *J Pediatr Endocrinol Metab* 2000;13:1537–1547.)

However, there are both congenital and acquired deficiencies of the 11b -HSD2 enzyme, so that the normal levels of cortisol remain fully active, flooding the mineralocorticoid receptor and inducing the full syndrome of mineralocorticoid excess: sodium retention, potassium wastage, and hypertension, with virtually complete suppression of renin and aldosterone secretion (Walker and Edwards, 1994).

11b-Hydroxysteroid Dehydrogenase Type 2 Deficiency: Apparent Mineralocorticoid Excess

Apparent mineralocorticoid excess (AME) is an autosomal recessive disorder that has now been identified in approximately 75 patients. The syndrome clinically is characterized by familial consanguinity, low birth weight, failure to thrive, onset of severe hypertension in early childhood with extensive target organ damage, hypercalciuria, nephrocalcinosis, and renal failure (Dave-Sharma et al., 1998; McTernan et al., 2001). As noted, sodium retention, hypokalemia, low aldosterone, and low renin levels are present.

Genetics

Soon after the first case of AME was described (Werder et al., 1974), Ulick et al. (1979) recognized that these children did not metabolize cortisol normally. Some years later, Stewart et al. (1988), in studies on a 20-year-old with the syndrome, recognized a defect in the renal cortisol-cortisone shuttle and demonstrated the deficiency of the 11b-HSD2 enzyme. A number of mutations in the 11b-HSD gene have now been identified in patients with AME (Cerame and New, 2000; Dave-Sharma et al., 1998; Nunez et al., 1999).

Some of these mutations result in only partial inhibition of the 11b-HSD2 enzyme, as evidenced by a higher ratio of urinary cortisone-to-cortisol metabolites and a milder clinical course with higher birth weight, later age of presentation (Nunez et al., 1999) and, in some patients (Rossi et al.), only mild low-renin hypertension (Wilson et al., 1998). Not surprisingly, mutations resulting in less inhibition of the enzyme have been sought in patients with “essential” hypertension. Some investigators have found them (Ferrari et al., 2000; Watson et al., 1996); others have not (Brand et al., 1998; Smolenicka et al., 1998).

Variant

A few patients with the features of AME have a defect not in the cortisol-to-cortisone shuttle but in the ring A reduction of cortisol to inactive metabolites, because of a deficiency of the 5b-reductase enzyme (Ulick et al., 1992a). The resultant high levels of cortisol keep the mineralocorticoid receptors flooded in the same manner as when 11b-HSD2 is deficient. In one family with classic AME, some affected patients also had reduced 5b–reductase activity (Morineau et al., 1999).

Therapy

Therapy is based on competitive blockade of the mineralocorticoid receptor with spironolactone (Dave-Sharma et al., 1998) and, hopefully in the near future, with the more selective blocker eplerenone (Funder, 2000). Suppression of endogenous cortisol with dexamethasone has also been used (Cooper and Stewart, 1998).

11b-Hydroxysteroid Dehydrogenase Type 2 Inhibition: Glycyrrhetinic Acid (Licorice)

Since the early 1950s, glycyrrhetinic acid, the active ingredient in licorice extract, has been known to cause hypertension, sodium retention, and potassium wastage. Stewart et al. (1987) and Edwards et al. (1988) recognized the similarities between the syndrome induced by licorice and the syndrome of AME and documented that licorice inhibited the same renal 11b-HSD2 enzyme that was deficient in AME. These effects are accompanied by a fall in cortisone and a rise in cortisol excretion, reflecting the inhibition of renal 11b-HSD2 activity.

Relatively small amounts of confectionery licorice, as little as 50 g daily for 2 weeks, produce a rise in BP in normotensive people (Sigurjonsdottir et al., 2001). The syndrome also has been induced by the licorice extracts in chewing tobacco and gum (Rosseel and Schoors, 1993). The diagnosis of licorice intake can be confirmed by an assay of urinary glycyrrhetinic acid (Kerstens et al., 1999).

The inhibition of 11b-HSD2 has been found to cause direct vascular effects (Quaschning et al., 2001) that could be involved in the severe target organ damages seen in patients with AME and, at the same time, support a role of extrarenal 11b-HSD2 in nongenomic effects of aldosterone (Alzamora et al., 2000).

Aldosterone receptor blockers relieve all the effects of licorice-induced hypertension (Quaschning et al., 2001).

Possible Additional Role

The potential for an expanded role of reduced 11b-HSD2 and 5b–reductase activity far beyond that related to ingestion of licorice has been raised (Walker, 2000). Reduced 11b-HSD2 activity has been reported in patients with chronic renal insufficiency (Watson et al., 1996), nephrotic syndrome (Vogt et al., 1999), low renin “essential” hypertension (Takeda et al., 1996), and hypertensive obese children (Csábi et al., 2000). However, inhibition of 11b-HSD2 has been seen with the flavonoids in grapefruit juice and tea (Guo and Reidenberg, 1998) so great care is needed in studies of the possible relationship between the inhibition of this enzyme and hypertension.

Massive Cortisol Excess

The capacity of the 11b-HSD-directed cortisol-cortisone shuttle and of 5b-reductase inactivation may be overcome by massive amounts of cortisol. Ulick et al. (1992b) found this to be responsible for the significant features of mineralocorticoid excess—profound hypokalemia and hypertension—seen in patients with ectopic ACTH tumors, wherein cortisol levels are much higher than in other causes of Cushing's syndrome.

Glucocorticoid Resistance

Among 60 hypertensive patients under age 36, 45 had increased levels of urinary glucocorticoid metabolites, suggesting partial resistance of glucocorticoid receptors with subsequent increased mineralocorticoid effects (Shamim et al., 2001).

DEOXYCORTICOSTERONE EXCESS: CONGENITAL ADRENAL HYPERPLASIA

Excessive amounts of the mineralocorticoid DOC may cause hypertension (Biglieri and Kater, 1991), arising either from hyperplastic adrenals with enzymatic deficiencies or from rare DOC-secreting tumors (Gröndal et al., 1990).

Defects in all the enzymes involved in adrenal steroid synthesis have been recognized. These defects are inherited in an autosomal recessive manner; the specific molecular defects are being recognized (Chabre et al., 2000; Pang, 1997). Their manifestations result from inadequate levels of the end products of steroid synthesis, particularly cortisol. The low levels of cortisol call forth increased secretion of ACTH, further increasing the accumulation of the precursor steroids proximal to the enzymatic block and stimulating steroidogenesis in pathways that are not blocked (Table 14-4).

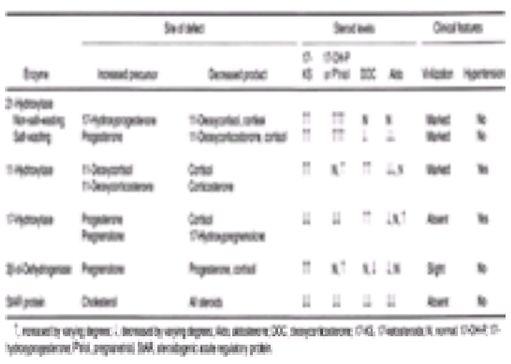

TABLE 14-4. *Syndromes of congenital adrenal hyperplasia*

The clinical manifestations of congenital adrenal hyperplasia (CAH), often obvious at birth, vary with the degree of enzymatic deficiency and the mix of steroids secreted by the hyperplastic adrenal glands. The most common type, the 21-hydroxylase deficiency, responsible for perhaps 90% of all CAH, is not associated with hypertension but is accompanied by a high prevalence of benign adrenal tumors (Ravichandran et al., 1996).

The two forms of CAH in which hypertension occurs are caused by deficiency of the 11b-hydroxylase (CYP11b1) or 17-hydroxylase (CYP17A) enzymes. Although these are rare causes of hypertension, partial enzymatic deficiencies have been observed in hirsute women (Lucky et al., 1986), so some hypertensive adults may have unrecognized, subtle forms of CAH.

11-Hydroxylase Deficiency

The 11-hydroxylase deficiency syndrome is usually recognized in infancy because, as shown in Figure 14-4, the defect sets off production of excessive androgens. The enzyme deficiency prevents the hydroxylation of 11-deoxycortisol, resulting in cortisol deficiency, and prevents the conversion of DOC to corticosterone and aldosterone. The high levels of DOC induce hypertension and hypokalemia, the expected features of mineralocorticoid excess. Thus, the syndrome features virilization of the infant, hypertension, and hypokalemia.

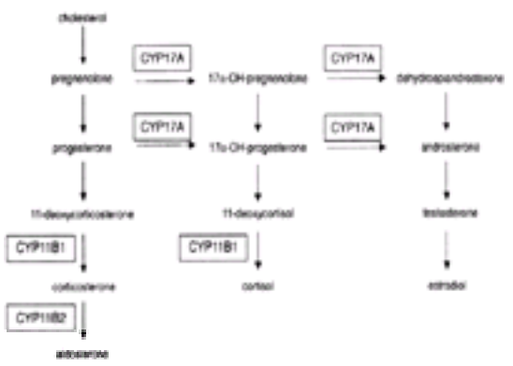

FIG. 14-4. The adrenal steroid pathway.

The enzyme deficiency has been attributed to various mutations in the *CYP 11B1* gene (Cerame and New, 2000; Hampf et al., 2001). The syndrome is diagnosed by finding high levels of 11-deoxycortisol and DOC in the urine and plasma. Treatment, as for all the syndromes of CAH, is with glucocorticoid, which should relieve the hypertension and hypokalemia and allow the child to develop normally. In those few whose disease cannot be controlled with glucocorticoid suppression, bilateral adrenalectomy has been required (Chabre et al., 2000).

17-Hydroxylase Deficiency

Unlike the 21-hydroxylase and 11-hydroxylase deficiencies, CAH caused by a 17-hydroxylase deficiency is associated with an absence of sex hormones, leading to incomplete masculinization in males and primary amenorrhea in females. Because 17-hydroxylase activity is also lacking in the gonads, the defect prevents conversion of the precursor pregnenolone into androgens and estrogens (Fig. 14-4). Although most affected 46XY males are phenotypically females, some may appear as partially virilized males at birth, presumably because they have less severe enzyme deficiency (Dean et al., 1984). The syndrome usually is not recognized until after the age of puberty when sexual development does not progress in a normal manner in patients who are phenotypically female. Only 120 or so cases have been recognized, but adolescents with hypertension and abnormal sexual development should be considered suspect (Hermans et al., 1996).

Now that the various renal and adrenal causes of hypertension have been covered, we shall turn to an even larger variety of less common forms.

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15
Other Forms of Secondary Hypertension

The preceding chapters covered the major types of hypertensive diseases listed in Table 1-6, accounting for perhaps 98% of the total. Others that deserve consideration are covered in this chapter. Coarctation, described in this chapter, and congenital adrenal hyperplasia, covered in Chapter 14, are seen mainly in children; additional coverage of hypertension in childhood is found in Chapter 16.

COARCTATION OF THE AORTA

Constriction of the lumen of the aorta may occur anywhere along its length but is seen most commonly just beyond the origin of the left subclavian artery, at or below the insertion of the ligamentum arteriosum. This lesion makes up approximately 7% of all congenital heart disease. Hypertension in the upper extremities with diminished or absent femoral pulses is the usual presentation (Table 15-1).

Symptoms
Headache
Cold feet
Pain in legs with exercise
Signs
Hypertension
Hyperdynamic apical impulse
Murmurs in front or back of chest
Pulsations in neck
Weak femoral pulse

TABLE 15-1. *Symptoms and signs of coarctation*

The traditional separation into infantile (pre-ductal) and adult (postductal) types is now considered inappropriate, with many preductal lesions not identified until adult life. As Jenkins and Ward (1999) state:

> A spectrum of lesions is now recognized, and it is only those with the most severe obstruction (e.g., aortic arch atresia or interruption) or associated cardiac defects who invariably present in infancy. Most other cases are now identified at routine medical examination. Otherwise, age at presentation is related to the severity rather than the site of obstruction, as a result of cardiac failure or occasionally cerebrovascular accident (CVA), aortic dissection, or endocarditis.

Natural History

If the coarctation is proximal to the ductus arteriosus, pulmonary hypertension, congestive failure, and cyanosis of the lower half of the body occur early in life. Before surgery was possible, 45% to 84% of infants found to have coarctation died during their first year of life (Campbell, 1970).

Patients with less severe postductal lesions may have no difficulties during childhood. However, they almost always develop premature cardiovascular disease; in the two largest series of autopsied cases seen before the advent of effective surgery, the mean age of death was 34 years (Campbell, 1970). The causes of death reflect the pressure load on the heart and the associated cardiac and cerebral lesions:

- Congestive heart failure, 25%
- Rupture of the aorta, 21%
- Bacterial endocarditis, 18%
- Intracranial hemorrhage, 11%

Mechanism of Hypertension

Beyond the obvious obstruction to blood flow, the coarctation may lead to a generalized increase in vascular resistance in tissues below the stenosis, suggesting a systemic vasoconstrictor mechanism (Liard and Spadone, 1985). In experimental models, the normotensive vessels below the aorta also thicken (Stacy and Prewitt,

1989), which could explain the persistence of arterial stiffness and hypertension after repair of the lesion (Guenthard and Wyler, 1995).

In experimental models, the renin-angiotensin system is inappropriately turned on in the presence of an expanded body fluid volume (Bagby and Mass, 1980). In patients, plasma renin levels may not be elevated under basal conditions, but both catechol and renin levels may rise excessively during exercise (Ross et al., 1992).

Recognition of Coarctation

Hypertension in the arms with weak femoral pulses in a young person strongly suggests coarctation. With minimal constriction, symptoms may not appear until late in life. Often the heart is large and shows left ventricular strain on the electrocardiogram. The chest radiograph can be diagnostic, demonstrating the “three” sign from dilation of the aorta above and below the constriction and notching of the ribs by enlarged collateral vessels. The diagnosis is now usually made by echocardiography and color Doppler flow mapping (Rao, 1995).

Atypical aortic coarctation in adults most likely represents Takayasu's arteritis, or pulseless disease, which usually affects the aortic arch and may also involve the descending aorta (Numano et al., 2000). This large-vessel vasculitis may be successfully treated with balloon angioplasty (Tyagi et al., 1992), but usually improves with corticosteroids (Numano et al., 2000).

Management

Surgery

If the disease is associated with other cardiac defects and induces heart failure in the first few weeks of life, early repair is necessary. If the infant is less afflicted, the operation should be performed electively between 6 and 12 months of age; if postponed, hypertension and left ventricular hypertrophy are more likely to persist, despite relief of aortic obstruction (Johnson et al., 1994). If the disease is milder and no troubles occur during infancy, surgery should be performed before age 9 (Cohen et al., 1989).

Immediately after surgical repair, the blood pressure (BP) may paradoxically rise. In most patients, this is transient and likely represents both renin-angiotensin and sympathetic nervous hyperactivity (Choy et al., 1987). For many patients, an upper-body hypertensive response to exercise may persist (Engvall et al., 1995). In approximately half of those patients whose coarctation was surgically repaired, plasma catecholamine and aldosterone levels remained elevated after an average of 8 years (Roegel et al., 1998).

The long-term outcome of patients after surgery for coarctation is certainly better than it is for those who do not undergo repair, but survival after surgery is less than in the general population (Bobby et al., 1991). The continuing risks involve arterial aneurysms in various sites, recurrence of coarctation, and persistence or recurrence of hypertension in as many as 70% of patients 30 years or longer after surgery (Jenkins and Ward, 1999). The prevalence of hypertension is related to the age of repair: 7% in patients undergoing surgery as infants, but 33% in those undergoing surgery after age 14 (Cohen et al., 1989).

Angioplasty

Balloon dilation angioplasty is being increasingly used and has become the treatment of choice (Fawzy et al., 1999). Stents are being used, both for recoarctation (Rosenthal et al., 1995) and as initial therapy (Ledesma et al., 2001).

HORMONAL DISTURBANCES

Hypothyroidism

Incidence

Among 40 patients prospectively followed over the time they became hypothyroid after radioiodine therapy for thyrotoxicosis, 16 (40%) developed a diastolic BP higher than 90 mm Hg (Streeten et al., 1988). These authors found hypothyroidism in 3.6% of 688 consecutively seen, referred hypertensive patients; the hypertension was reversed in one-third of these patients given thyroid hormone replacement therapy. However, others found no differences in diastolic BP in 122 elderly patients with elevated thyroid-stimulating hormone levels, averaging 13.8 mU per L, as compared to the BPs in euthyroid controls (Bergus et al., 1999).

Mechanism of Hypertension

Hypothyroid patients tend to have a low cardiac output with a decrease in contractility and impaired diastolic relaxation (Biondi et al., 1999). To maintain tissue perfusion, peripheral resistance increases, from a combination of increased responsiveness of a-adrenergic receptors and an increased level of sympathetic nervous activity (Fletcher and Weetman, 1998). These would tend to raise diastolic BPs more than systolic BPs, the usual pattern seen in hypothyroidism (Saito and Saruta, 1994). The hypertension often responds to a low-sodium diet (Marcisz et al., 2001).

Hyperthyroidism

An elevated systolic but lowered diastolic BP is usual in patients with hyperthyroidism. This pat-tern is associated with a high cardiac output and reduced peripheral resistance (Fraser et al., 1989).

Hyperparathyroidism

Primary hyperparathyroidism (PHPT), once seen only as a symptomatic disease with significant hypercalcemia, is now most commonly recognized in asymptomatic patients with minimally elevated serum calcium levels (Silverberg, 2000). Often the hypercalcemia is noted only after thiazide therapy is started.

Hypertension is common in PHPT (Toft, 2000). Patients have increased arterial stiffness (Smith et al., 2000) and impaired endothelium-mediated vasodilation (Nilsson et al., 1999), which may (Kosch et al., 2000) or may not (Neunteufl et al., 2000) improve after surgical relief of PHPT. Moreover, no correlation was found between serum calcium or parathyroid hormone levels and BP in 194 PHPT patients (Lumachi et al., 2000). Perhaps not surprisingly, hypertension usually does not recede after surgical relief (Silverberg, 2000), although left ventricular hypertrophy usually regresses (Stefenelli et al., 1997).

Even if hypertension is not relieved, parathyroidectomy may be indicated for relief of psychiatric manifestations (Velasco et al., 1999), coexisting diabetes (Richards and Thompson, 1999), and bone demineralization (Toft, 2000), particularly as preoperative localization (De Feo et al., 2000) and minimally invasive surgery (Chen et al., 1999) are now feasible.

Pseudohypoparathyroidism

Half of a group of adults with pseudohypoparathyroidism type I, caused by target organ resistance to parathyroid hormone, were hypertensive (Brickman et al., 1988).

Acromegaly

Hypertension is found in approximately 35% of patients with acromegaly because of sodium retention caused by the high levels of growth hormone (Gomberg-Maitland and Frishman, 1996), increased sympathetic vasoconstriction, and reduced endothelium-dependent vasodilation (Maison et al., 2000). Left ventricular hypertrophy and impaired systolic function are usual, a consequence of a specific acromegalic cardiomyopathy that is aggravated by hypertension (Colao et al., 2000). Cardiovascular risks are further increased by a high prevalence of sleep apnea (Weiss et al., 2000).

Acromegaly has usually been treated by transsphenoidal surgery, but depot somatostatin analogs or a genetically engineered growth hormone receptor antagonist

may become the first line of therapy (Utiger, 2000).

SLEEP APNEA

Sleep-disordered breathing, defined as repeated episodes of apnea and hypopnea during sleep, was found in 9% of women and 24% of men in a random sample of 602 employed people aged 30 to 60 years (Young et al., 1993). In the total population, 2% of women and 4% of men met the criteria for the *sleep apnea syndrome*, defined as "an apnea-hypopnea score of at least five episodes lasting 10 s or more per hour of sleep plus daytime hypersomnolence" (Young et al., 1993). Roux et al. (2000) estimate that sleep apnea is present in 12 million people aged 30 to 60 years in the United States and in another 7.5 million older than 65 years. The syndrome is significantly underrecognized (Piccirillo et al., 2000) and is likely increasing in prevalence in association with obesity (Vgontzas et al., 2000).

Clinical Features and Diagnosis

Most sleep apnea is due to upper airway obstruction. Sleep apnea should be considered in patients with the clinical features of increasing obesity, loud snoring, fitful sleep, and daytime sleepiness (Table 15-2). Virtually all with sleep apnea will snore, but only approximately half of people who snore for more than half the night have sleep apnea (Ferini-Strambi et al., 1999). The diagnosis can be made by a sleep study at home (Chervin et al., 1999) but with more certainty by overnight polysomnography in a sleep laboratory, with continuous recordings of respiration, electroencephalogram, electromyogram, eye movements, electrocardiogram, O_2 saturation, and BP.

History	
Snoring*	
Apnea during sleep	
Arousals or awakenings	
Choking spells	
Nocturnal diaphoresis or enuresis	
Abnormal motor activity during sleep	
Excessive daytime sleepiness*	
Headaches	
Loss of memory and concentration	
Personality changes, depression	
Angina	
Diminished libido, impotence	
Physical examination	
Hypertension*	
Overweight, particularly visceral*	
Oral cavity abnormalities	
Enlarged tonsils	
Thickened uvula	
Long and redundant soft palate	
Cardiovascular findings	
Increased heart rate variability	
Left ventricular hypertrophy	
Arrhythmias	
Conduction disturbances	

*Most useful in considering diagnosis.

TABLE 15-2. *Clinical features of obstructive sleep apnea*

Association with Hypertension

Incidence

Multiple cross-sectional and observational studies have unequivocally shown a higher prevalence and incidence of systemic hypertension in direct proportion to the severity of sleep apnea. In recent reports, the odds ratio (OR) for hypertension among patients with sleep apnea has been found to vary from as little as 1.37 (Nieto et al., 2000) to 2.4 (Bixler et al., 2000) to 2.89 (Peppard et al., 2000a) to 4.15 (Grote et al., 1999). Increasing ORs are seen with increasing levels of sleep apnea. Lavie et al. (2000) found that each apneic event per hour of sleep increased the odds for hypertension by 1%, whereas each 10% decrease in O_2 saturation increased the odds by 13%.

A history of snoring, by itself, has been associated with an increased incidence of hypertension. Among 73,000 U.S. female nurses followed for 8 years, the risk of developing hypertension increased by 29% in those who snored occasionally and by 55% in those who snored regularly as compared to those who said they did not snore (Hu et al., 1999). The association was independent of age, body mass index, waist circumference, and other lifestyle factors.

The risk of hypertension is greater for younger subjects than for those older than 60 years (Bixler et al., 2000) and is independent of all other relevant risk factors (Lavie et al., 2000). Moreover, the prevalence of sleep apnea is higher both in patients with uncontrolled hypertension (Grote et al., 2000), and in patients with stroke (Mohsenin, 2001).

Mechanisms of Hypertension

The rather ancient scheme shown in Figure 15-1 still seems to explain the hypertension seen with sleep apnea, except that the question mark for sustained hypertension should be removed. On the other hand, as will be noted, relief of sleep apnea will relieve the hypertension, so perhaps the question mark is appropriate.

FIG. 15-1. Proposed mechanism for cyclic systemic hypertension with sleep apnea that may lead to sustained hypertension. pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen. (Modified from Schroeder JS, Motta J, Guilleminault C. *Sleep apnea syndromes*. New York: Liss, 1978.)

Increased sympathetic nervous activity (Narkiewicz and Somers, 1999) and increased levels of endothelin-1 (Phillips et al., 1999) have been measured in patients with sleep apnea, along with a blunted vasodilation in response to various stimuli (Duchna et al., 2000) and increased levels of soluble cell adhesion molecules (Chin et al., 2000).

Treatment

Weight loss (Karason et al., 2000)—even as little as 10% of body weight (Peppard et al., 2000b)— and regular exercise (Sherrill et al., 1998) will help over the long term; avoiding the supine position during sleep by taping a tennis ball to the back will help in the short-term (Berger et al., 1997). The best relief is by nasal continuous positive airway pressure, which has been shown in placebo-controlled trials to relieve symptoms (Jenkinson et al., 1999) and lower nighttime BPs (Dimsdale et al., 2000), converting "nondippers" into "dippers" (Akashiba et al., 1999) and reducing nocturnal BP in women with preeclampsia (Edwards et al., 2000).

These effects on BP are accompanied by decreases in daytime sympathetic nerve traffic (Narkiewicz et al., 1999) and improved vasodilator responses (Leuenberger

et al., 2000).

If the hypertension persists, antihypertensive drugs should be used. In a sequential study of one agent each from five classes of drugs, each given for 6 weeks to 40 hypertensives with obstructive sleep apnea, atenolol, 50 mg per day, provided greater lowering of both office and 24-hour ambulatory BP than did amlodipine, enalapril, losartan, or hydrochlorothiazide (Kraiczi et al., 2000). This better response to a b-blocker is in keeping with the known involvement of increased sympathetic nervous activity in the causation of obstructive sleep apnea–induced hypertension. No effects on sleep-disordered breathing or day-time well-being were noted with any of the drugs.

NEUROLOGIC DISORDERS

A number of seemingly different disorders of the central and peripheral nervous system may cause hypertension. Many may do so by a common mechanism involving sympathetic nervous system discharge from the vasomotor centers in response to an increased intracranial pressure. The rise in systemic pressure is useful in restoring cerebral perfusion (Plets, 1989).

As noted in Chapter 4 and Chapter 7, patients with acute stroke may have transient marked elevations in BP. Rarely, episodic hypertension suggestive of a pheochromocytoma may occur after cerebral infarction (Funck-Brentano et al., 1987).

Brain Tumors

Intracranial tumors, especially those arising in the posterior fossa, may cause hypertension (Pallini et al., 1995). In some patients, paroxysmal hypertension and other features that suggest catecholamine excess may point mistakenly to the diagnosis of pheochromocytoma (Bell and Doig, 1983). The problem may be confounded by the increased incidence of neuroectodermal tumors, some within the central nervous system, in patients with pheochromocytoma. Unlike patients with a pheochromocytoma who always have high catechol levels, patients with a brain tumor may have increased catecholamine levels during a paroxysm of hypertension but normal levels at other times.

Quadriplegia

Patients with transverse lesions of the cervical spinal cord above the origins of the thoracolumbar sympathetic neurons lose central control of their sympathetic outflow. Stimulation of nerves below the injury, as with bladder or bowel distension, may cause reflex sympathetic activity via the isolated spinal cord, inducing hypertension, sweating, flushing, piloerection, and head-ache, a syndrome described as *autonomic hyperreflexia*. Such patients have markedly exaggerated pressor responses to various stimuli (Krum et al., 1992).

The hypertension may be severe and persistent enough to cause cerebrovascular accidents and death. During hypertensive episodes in five patients whose mean arterial BP rose from 95 to 154 mm Hg, the heart rate fell from 72 to 45, cardiac output was unchanged, and peripheral resistance rose markedly (Naftchi et al., 1978). Plasma volume was reduced by 10% to 15%, which may explain the propensity of these patients to develop hypotension when the hypertensive stimulus is removed. An a-blocker effectively controlled the syndrome (Chancellor et al., 1994).

Severe Head Injury

Immediately after severe head injury, the BP may rise because of a hyperdynamic state mediated by excessive sympathetic nervous activity (Simard and Bellefleur, 1989). If the hypertension is persistent and severe, a short-acting b-blocker (e.g., esmolol) should be given. Caution is needed in the use of vasodilators such as hydralazine and nitroprusside, which may increase cerebral blood flow and intracranial pressure (Van Aken et al., 1989). Moreover, hypotension is an even greater threat (Winchell et al., 1996).

Other Neurologic Disorders

Hypertension may be seen with

- Guillain-Barré syndrome (Minami et al., 1995).
- Fatal familial insomnia, a prion disease with severe atrophy of the thalamus (Portaluppi et al., 1994).
- Baroreceptor failure, controllable by clonidine (Robertson et al., 1993).
- Autonomic failure with orthostatic hypotension and supine hypertension, often helped by bedtime transdermal nitroglycerin (Shannon et al., 1996).

Unlike the situation in many neurologic diseases, hypertension is less common in patients with Alzheimer's disease, apparently receding as the process worsens, even without an associated weight loss (Morris et al., 2000).

PSYCHOGENIC HYPERVENTILATION

Anxiety is diagnosed almost 5 million times a year in office visits to physicians in the United States (Skaer et al., 2000). As common as it is, anxiety and its manifestations are often not recognized as being responsible for a variety of symptoms. Because of the common failure to recognize the underlying nature of various functional syndromes (Wessely et al., 1999) (Table 15-3), patients and their physicians often enter into a vicious cycle: more and more testing, often with false-positive results; more and more incorrect “organic” disease diagnoses; more and more ineffective therapy; more and more anxiety; and more and more functional symptoms.

Specialty	Syndrome
Gastroenterology	Irritable bowel syndrome, non-ulcer dyspepsia
Gynecology	Premenstrual syndrome, chronic pelvic pain
Rheumatology	Fibromyalgia
Cardiology	Atypical or noncardiac chest pain
Respiratory medicine	Hyperventilation syndrome
Infectious diseases	Chronic (postviral) fatigue syndrome
Neurology	Tension headache
Dentistry	Temporomandibular joint dysfunction, atypical facial pain
Ear, nose, and throat	Globus syndrome
Allergy	Multiple chemical sensitivity

Reprinted from Wessely S, Nimnuan C, Sharpe N. Functional somatic syndromes: one or many? *Lancet* 1999;354:936–939, with permission.

TABLE 15-3. *Functional somatic syndromes by specialty*

As noted in Chapter 4, the problem is often encountered with hypertensive patients, either because of their concern over having “the silent killer” or because of their poor response to antihypertensive therapies. In 300 consecutive patients referred to me, usually because of hypertension that was difficult to control, 104 had symptoms attributable to anxiety-induced hyperventilation (Kaplan, 1997) (Fig. 15-2). The symptoms and signs of panic attack encompass all these same manifestations but go beyond them to include fears of falling apart, losing control, or even more acute anxiety (Hegel and Ferguson, 1997).

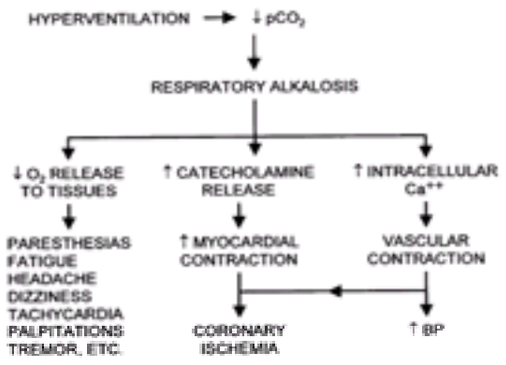

FIG. 15-2. The mechanisms by which acute hyperventilation may induce various symptoms, coronary ischemia, and a rise in blood pressure(BP). Ca, calcium; pCO_2, partial pressure of carbon dioxide.

Many of these patients had been subjected to intensive workup for dizziness, headaches, chest pain, fatigue, and the like. In only a small number had the referring physicians considered the functional nature of their symptoms. When the symptoms are reproduced by voluntary over-breathing and relieved by rebreathing into a paper sack, the patient's recognition of the mechanism often provides immediate relief and opens the way to the appropriate use of rebreathing exercises, other cognitive therapy or, if needed, antianxiety medications.

My experience is not unique. Among 351 hypertensive patients randomly selected from one primary care practice in Sheffield, United Kingdom, panic attacks had occurred in 18% during the previous 6 months and in 37% over their lifetime (Davies et al., 1999). The reported diagnosis of hypertension usually antedated the onset of panic attacks. Mann (1999) described 21 patients with severe, symptomatic paroxysmal hypertension that had usually been attributed to a pheochromocytoma but that was emotionally provoked and was relieved by antianxiety therapies.

In patients who have experienced panic attacks, the BP rises significantly during voluntary hyperventilation, unlike a tendency for the BP to go down during hyperventilation in subjects who have not had panic attacks (Martinez et al., 1998). Moreover, they tend to have more distress and slower recovery from hypocapnia during voluntary hyperventilation (Wilhelm et al., 2001).

The scenario is obvious: Anxiety over hypertension may lead to more hypertension; failure to recognize the functional nature of the symptoms may lead to more anxiety, and on and on. A direct correlation between levels of anxiety, measured by the Spielberger Inventory Trait, and BP has been observed (Paterniti et al., 1999). As noted in Chapter 3, anxiety from psychological stress may be involved in the genesis of hypertension. Hypertension can also be responsible for more anxiety. Of further interest, Gratacòs et al. (2001) found a gene duplication on chromosome 15 in 90% of patients with anxiety disorders so that other connections with hypertension may be involved.

ACUTE PHYSICAL STRESS

Hypertension may appear during various acute physical stresses, usually reflecting an intense sympathetic discharge and sometimes the contribution of increased renin-angiotensin from volume contraction. Problems related to anesthesia and surgery are covered in Chapter 7.

Medical Conditions

Significant hypertension has been observed in patients with various acutely stressed medical conditions, including the following:

- Hypoglycemia, particularly if it develops in diabetics receiving noncardioselective b-blockers, wherein a-mediated vasoconstriction may be unopposed (Lloyd-Mostyn and Oram, 1975)
- Acute pancreatitis (Greenstein et al., 1987)
- Acute intermittent porphyria (Andersson et al., 2000)
- After exposure to cold (Wilmhurst et al., 1989)
- Acute respiratory distress in patients with chronic obstructive pulmonary disease (Fontana et al., 2000)

Unlike most patients who are in acute pain, patients with acute, painful vasoocclusive crises of sickle-cell disease have *lower* BP than is seen in patients without sickle-cell disease (Ernst et al., 2000).

Surgical Conditions

Burns

Hypertension appears in approximately 25% of patients with significant second and third-degree burns (Brizio-Molteni et al., 1979). The BP usually rises within 3 to 5 days, may last 2 weeks, and occasionally induces encephalopathy (Lowrey, 1967).

Perioperative Hypertension

In addition to the reasons mentioned in the coverage of anesthesia and hypertension in Chapter 7, for numerous reasons hypertension may be a problem during and soon after surgery. For example, the application of a tourniquet during lower-limb surgery was accompanied by hypertension in 11% of patients (Kaufman and Walts, 1982). In 60 patients with transient postoperative readings in excess of 190/100 mm Hg in the recovery room, the probable causes were pain (36%), hypoxia and hypercapnia (19%), and physical and emotional excitement (32%) (Gal and Cooperman, 1975). As noted in Chapter 8, these causes should be managed rather than treating the BP with anti-hypertensives, and especially not with sublingual nifedipine.

Surprisingly, marked rises in BP have been measured when pneumoperitoneum is per-formed for abdominal laparoscopic surgery (Joris et al., 1998). The rise in BP was accompanied by increases in blood catecholamines, cortisol, and vasopressin and was blunted by preoperative clonidine.

Cardiovascular Surgery

Table 15-4 summarizes the causes of hypertension associated with surgery in a temporal fashion (Estafanous and Tarazi, 1980; Vuylsteke et al., 2000).

Preoperative
Anxiety, angina
Discontinuation of antihypertensive therapy
Rebound from β-blockers in patients with coronary artery disease
Intraoperative
Induction of anesthesia: tracheal intubation; nasopharyngeal, urethral, or rectal manipulation
Before cardiopulmonary bypass (during sternotomy and chest retraction)
Cardiopulmonary bypass
After cardiopulmonary bypass (during surgery)
Postoperative
Early (within 2 h)
Obvious cause: hypoxia, hypercapnia, ventilatory difficulties, hypothermia, shivering, arousal from anesthesia
With no obvious cause; after myocardial revascularization; less frequently after valve replacement; after resection of aortic coarctation
Late (weeks to months)
After aortic valve replacement by homografts

Data from Estafanous FG, Tarazi RC. Systemic arterial hypertension associated with cardiac surgery. *Am J Cardiol* 1980;46:685–694.

TABLE 15-4. *Hypertension associated with cardiac surgery*

Coronary Bypass

Approximately one-third of patients will have hypertension after coronary artery bypass grafting, usually starting within the first 2 hours after surgery and lasting 4 to 6 hours. The hypertension likely reflects an increase in peripheral resistance resulting from sympathetic overactivity (Leslie, 1993). Immediate therapy may be important to prevent postoperative heart failure or myocardial infarction. In addition to deepening of anesthesia, various parenteral antihypertensives have been used, including nitroprusside and nitroglycerin (Vuylsteke et al., 2000).

Other Cardiac Surgery

Hypertension has been reported, although less frequently, after other cardiac surgery, including closure of atrial septal defects (Cockburn et al., 1975) and valve replacement (Estafanous et al., 1978). Closure of a peripheral arteriovenous shunt may precipitate acute hypertension by various mechanisms, including activation of the reninangiotensin mechanism (Rocchini et al., 1978).

Virtually all patients who undergo heart transplantation develop hypertension and lose the usual nocturnal fall in BP, likely from a combination of effects, including the effects of immunosuppressive agents (see the section Cyclosporine and Tacrolimus, later in this chapter), impaired baroreceptor control from cardiac denervation, and inability to excrete sodium normally (Jenkins and Singer, 1998; Leenen et al., 1998).

The hypertension may be controlled by either angiotensin-converting enzyme inhibitors or calcium channel blockers as monotherapy, each effective in approximately half of patients (Brozena et al., 1996).

Carotid Endarterectomy

Postoperative hypertension may be particularly serious in patients with known cerebrovascular disease who have carotid endarterectomy, per-haps because of increased baroreceptor sensitivity (Hirschl et al., 1993). Treatment most logically should be with either of the short-acting b-blockers esmolol or labetalol (Orlowski et al., 1988) rather than with a vasodilator that might further increase cerebral blood flow.

INCREASED INTRAVASCULAR VOLUME

If vascular volume is raised a significant degree over a short period, the renal natriuretic response may not be able to excrete the excess volume, particularly if renal function is also impaired.

Erythropoietin Therapy

Recombinant human erythropoietin is now being widely used to correct the anemia of chronic renal failure. As the hematocrit rises, so do blood viscosity and BP; nearly one-third of patients developed clinically important hypertension (Clyburn and DiPette, 1995). Ni et al. (1998) found that erythropoietin-induced hypertension was independent of the rise in hematocrit but was accompanied by increases in cytosolic calcium and resistance to nitric oxide, effects that were ameliorated by a calcium channel blocker.

Polycythemia and Hyperviscosity

Patients with primary polycythemia are often hypertensive, and some hypertensives have a relative polycythemia that may resolve when the BP is lowered (Chrysant et al., 1976). A high hematocrit may significantly reduce cerebral blood flow, which puts the patient at additional risk (Hudak et al., 1986). With venesection and a fall in hematocrit, cerebral blood flow increases (Humphrey et al., 1979).

The hypertension seen in polycythemic states could also reflect increased blood viscosity. Significant falls in BP were seen in 12 hypertensive patients with polycythemia when blood viscosity was reduced without changing blood volume (Bertinieri et al., 1998).

After Transfusions and Marrow Transplants

A syndrome of hypertension, convulsions, and cerebral hemorrhage was seen in eight patients with thalassemia after multiple blood transfusions (Wasi et al., 1978). Because the episodes often developed days after the transfusions, they were considered not to be caused by volume overload, but rather, by the presence of unknown vasopressor substances. Similar episodes have been reported in others receiving multiple trans-fusions, particularly in the presence of renal insufficiency (Eggert and Stick, 1988).

Hypertension has developed after autologous bone marrow transplantation (Sugarman et al., 1990) and is seen in 75% of those who are given cyclosporine and other immunosuppressants with allogeneic bone marrow transplants (Kone et al., 1988).

Inappropriate Antidiuretic Hormone

Hypertension has been reported in patients with inappropriate secretion of antidiuretic hormone and is presumably related to an overexpanded vascular volume (Whitaker et al., 1979).

CHEMICAL AGENTS THAT CAUSE HYPERTENSION

Table 15-5 lists various chemical agents that may cause hypertension, indicating their mechanism if known. Some of these substances, such as sodium-containing antacids, alcohol, insulin, licorice, oral contraceptives, and monoamine oxidase inhibitors, are covered elsewhere in this book because of their frequency or special features.

TABLE 15-5. *Hypertension induced by chemical agents*

Cyclosporine and Tacrolimus

The introduction of cyclosporine in 1983 greatly improved the long-term survival of patients undergoing organ transplantation. However, major complications soon became obvious: nephrotoxicity and hypertension, which were assumed to be connected, and hepatotoxicity.

Hypertension develops after weeks or months in 25% to 95% of patients given cyclosporine, most commonly after heart trans-plantation (Jenkins and Singer, 1998). Despite hopes that tacrolimus (FK506) would be less of a problem, it causes as much hypertension as does cyclosporine (Takeda et al., 1999) and, at least in liver transplant recipients, even more nephrotoxicity (U.S. Multicenter FK506 Liver Study Group, 1994).

Mechanism

A number of abnormalities have been blamed for cyclosporine-induced hypertension, including activation of sympathetic nervous activity (Ryuzaki et al., 1997), blunted natriuretic response to volume expansion (Braith et al., 1996), impaired nitric oxide–mediated vasodilation (Oriji and Keiser, 1999), and activation of endothelin release (Vogel et al., 1997). Because BP rises immediately after a single dose and is followed by transient natriuresis, neither renal dysfunction nor sodium retention are the initiating factors (Hansen et al., 1997).

The basic fault may involve a molecular mechanism that mediates both the immunosuppressive and the hypertensive actions of these drugs. Sander and co-workers (1996) noted that these agents bind to a recently discovered class of cytoplasmic receptors (immunophilins) present on various cells including T lymphocytes. Binding of cyclosporine to these receptors leads to inhibition of calcineurin, the calcium-calmodulin-dependent protein phosphatase. The inhibition of calcineurin was subsequently found to activate renal sympathetic afferent nerves (Zhang and Victor, 2000).

Treatment

Whatever the mechanism, calcium channel blockers seem to prevent many of the adverse effects of cyclosporine (Sánchez-Lozada et al., 2000). Although angiotensin-converting enzyme inhibitors may not be quite as effective in lowering BP, they may protect the kidneys from fibrosis (Shihab et al., 1996).

Other Agents

Perhaps the most commonly encountered form of chemically induced hypertension is that related to the use of foods and drugs containing large amounts of sodium. More dramatic effects are seen with the use of sympathomimetic agents. Large amounts of these drugs, available over the counter as herbal remedies (Haller and Benowitz, 2000) and for use as nasal decongestants (e.g., pseudoephedrine) and, until recently, as appetite suppressants (e.g., phenylpropanolamine), may raise the BP enough to induce, on rare occasions, hypertensive encephalopathy, strokes, and heart attacks (Kernan et al., 2000; Lake et al., 1990). In usual doses, however, pseudoephedrine does not raise BP, even in patients receiving b-blockers (Mores et al., 1999).

The multiple interferences with the effectiveness of various antihypertensive agents are covered in Chapter 7. Nonsteroidal antiinflammatory drugs may interfere with the effects of virtually all antihypertensive drugs. Tricyclic antidepressants may induce postural hypotension or supine hypertension and interfere with the antihypertensive effect of certain drugs (Walsh et al., 1992). The newer, reversible inhibitors of monoamine oxidase A, such as moclobemide, are less likely to incite pressor effects with tyramine-containing foods (Laux et al., 1996).

Of particular concern is the rapid increase in uncontrolled use of herbal remedies, some containing ephedrine, yohimbine, licorice, or other ingredients that may raise BP and interfere with the effectiveness of antihypertensive therapy (Fugh-Berman, 2000; Haller and Benowitz, 2000).

Perhaps the safest way to prevent these various interactions is to advise hypertensives to avoid all over-the-counter drugs and herbal remedies and to inform their physicians who prescribe other medications about their antihypertensive drug regimens.

Street Drugs

Marijuana, or d-9-tetrahydrocannabinol, in moderate amounts will increase the heart rate but usually lowers the BP (Hollister, 1986) and appears not to hasten cognitive decline (Lyketsos et al., 1999).

Heroin and other drugs taken intravenously may lead to severe renal damage, likely from an immunologic response (Rao et al., 1974).

Cocaine (Nzerue et al., 2000) and amphetamines (Lester et al., 2000) may cause transient but significant hypertension that may cause strokes and serious cardiac damage. Most cocaine-related deaths are associated with myocardial injury similar to that seen from catecholamine excess and aggravated by acute hypertension. Chronic cocaine abuse does not appear to induce hypertension (Brecklin et al., 1998) but may be associated with chronic renal disease (Norris et al., 2001; Nzerue et al., 2000).

The next and last chapter, written by Dr. Ellin Lieberman, looks further at hypertension in children and adolescents.

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16
Hypertension in Childhood and Adolescence

A separate discussion devoted to pediatric hypertension is required in a book focused on adults because of the following:

- Many physicians care for children and adults.
- Criteria for the diagnosis and management of hypertension in young people are based on techniques and data that differ from those used in adults.
- Techniques for the evaluation and treatment of children and of adolescents also differ.
- The existence of primary (essential) hypertension in parents has important implications for their offspring.
- Primary hypertension most likely has its origins in childhood and in adolescence.
- Early attention to cardiovascular risk factors during the first two decades of life may prevent or slow the development of vascular complications associated with hypertension.

This chapter focuses on the problems of measurements and of interpretation of blood pressure (BP) levels in children; on the significance of elevated BP levels; and on special issues, including neonatal hypertension, reflux nephropathy, and hypertensive emergencies. A discussion of most major nonrenal causes has been excluded because they are covered elsewhere in this text: coarctation of the aorta in Chapter 15, adrenocortical disorders in Chapter 13 and Chapter 14, and pheochromocytoma in Chapter 12. Emphasis is given to the need to recognize and deal with the psychosocial burdens imposed by the diagnosis and management of hypertension in young patients.

The universe of pediatric hypertension has recently undergone dramatic changes, as described in multiple reviews [Bartosh and Aronson, 1999; Flynn, 2001; Kay et al., 2001; National High Blood Pressure Education Program (NHBPEP), 1996; Sinaiko, 1996]. The use of ambulatory BP monitoring (ABPM) as an important adjunct has been highlighted (Lurbe and Redon, 2000; Sorof et al., 2000; Sorof and Portman, 2000). More information concerning the epidemiology, evaluation, and treatment of childhood hypertension is available so that clinicians have a more solid basis for clinical decision making, although long-term outcome data are still lacking.

BLOOD PRESSURE MEASUREMENT

Routine BP measurements should be obtained by age 3 years and yearly thereafter. Patterns of BP should be monitored along with weight, because body mass index (BMI) increases are recognized as powerful determinants of BP elevation beginning in childhood and continuing into adulthood.

Sphygmomanometry

Accurate recording and interpretation of BP levels in infants, children, and adolescents require the use of appropriate equipment, agreement concerning which Korotkoff sounds are used for diastolic BP (DBP) and, most important, the availability of adequate data from large numbers of normal children examined with similar techniques. The following is an adaptation for children of the portion of Chapter 2 that deals with BP measurements in adults.

Technique

The fewest errors result if the observer uses the recommended techniques and records the levels, the position of the child, and the size of the cuff used. The mercury manometer should be at the observer's eye level to avoid errors introduced by parallax, and the child's arm should be at heart level.

The NHBPEP's 1996 update of the 1987 task force's recommendations outlines in detail the process required for accurate BP recordings in children and adolescents. An important change in recommendations is that the fifth Korotkoff sound (K5) be used as the best indirect reflection of DBP throughout childhood and adolescence.

However, a study from Berenson's group (Elkasabany et al., 1998) suggests that childhood K4 values have greater reliability for correlation with adult K5. Of an initial study group of 12,139, 20% had repetitive measurements during childhood, adolescence, and young adulthood (ages 19 to 32 years). K5 was a less reproducible measure of DBP at younger ages, and K4 was a more reliable predictor of adult K5. Data from other comparable longitudinal studies are needed to validate these findings.

The other change in recommended technique concerns the choice of cuff size in relation to the right upper arm, used by convention in pediatrics. The cuff bladder width should be approximately 40% of the circumference of the arm when measured at a point between the olecranon and acromion. The cuff bladder should cover 80% to 100% of the circumference of the arm. Multiple cuff sizes are available to adjust for different arm sizes in a young population. If the ideal cuff is not available, use of a larger cuff is recommended to avoid spuriously high readings (Moss, 1981).

Children, especially toddlers, require time to relax and to familiarize themselves with their surroundings and with the examiner. Young children feel more in control when sitting and, therefore, are less anxious in that position than when supine. Nonetheless, Korotkoff sounds are often difficult to hear, because they are softer in children than in adults.

Auscultation is the most common technique used for BP measurements in clinical practice. Oscillometric recordings, however, are often used in hospital and emergency room settings. The complexities of BP measurements using sphygmomanometry and oscillometry have recently been emphasized (Goonasekera and Dillon, 2000). Park et al. (2001) compared results of BP recordings of 7,208 youngsters, aged 5 to 17 years, using the automatic Dinamapp model 8100 with traditional auscultation [using K1 for systolic BP (SBP) and K5 for DBP]. The authors found that the Dinamapp averaged 10 mm Hg higher for SBP and 5 mm Hg higher for DBP. If these results are confirmed, automatic BP recordings will need to be standardized against auscultation to avoid speciously high measurements.

Doppler ultrasonography with an appropriately sized cuff is routinely used in neonates (Groble, 1993). SBP is recorded when the intensity of reflected sound waves increases; continued deflation results in a distinct muffling, which is interpreted as the DBP. This method provides data comparable to other noninvasive, indirect

procedures and direct intraarterial measurements. However, accuracy of this method for DBP levels remains undocumented (Weismann, 1988).

Interpretation

Consensus exists concerning the interpretation of BP levels in children and adolescents, with BP percentiles being based not only on gender and age but also on height (Table 16-1). Although only the first BP reading was used to derive the BP norms shown in Table 16-1, data from more than 60,000 children of diverse ethnicities were included. This classification accepts levels of SBP and DBP below the ninetieth percentile as normal, those between the ninetieth and ninety-fifth percentiles as high-normal, and those repeatedly at or above the ninety-fifth percentile as hypertension.

Blood pressure (mm Hg)	Age (yr)	Height percentile for boys				Height percentile for girls			
		5	25	75	95	5	25	75	95
Systolic	3	104	107	111	113	104	105	108	110
	6	109	112	115	117	108	110	112	114
	10	114	117	121	123	116	117	120	122
	13	121	124	128	130	121	123	126	128
	16	129	132	136	138	125	127	130	132
Diastolic	3	63	64	66	67	65	65	67	68
	6	72	73	75	76	71	72	73	75
	10	77	79	80	82	77	77	79	80
	13	79	81	83	84	80	81	82	84
	16	80	84	86	87	83	83	85	86

[a]The height percentiles were determined from standard growth curves.
Data from the National High Blood Pressure Education Program Working Group on Hypertension in Children and Adolescents. Update on the task force report (1987) on high blood pressure in children and adolescents. Pediatrics 1996;98:649–658.

TABLE 16-1. *Ninety-fifth percentile of blood pressure in boys and girls 3 to 16 years of age, according to height*[a]

Table 16-1 lists only the ninety-fifth percentiles of BP by different percentiles of height at selected ages, the levels to be considered as indicating the presence of hypertension. The ninetieth percentiles of BP, the level for a high-normal classification, are almost all 4 mm Hg lower than the ninety-fifth percentiles.

Ambulatory Blood Pressure Monitoring

Numerous studies on the use of ABPM in young individuals have recently been published (Barker et al., 2000; Flynn, 2000a; Khan et al., 2000; Lurbe and Redon, 2000; Sorof and Portman, 2000). High prevalences of white-coat hypertension, from 44% to 88%, have been reported in children, but similar thresholds for ABPM have been used as office readings, whereas in adults the ABPM thresholds are considerably lower (see Chapter 2). Before ABPM can be widely accepted in clinical practice, the following issues need resolution: agreement about techniques, provision of normative data, and guidelines for the definition of ABPM hypertension.

Nonetheless, ABPM has been shown to help clinicians distinguish between an isolated, casual abnormal measurement (i.e., white-coat hypertension) and a 24-hour normal pattern (Khan et al., 2000; Koch et al., 1999; Sorof and Portman, 2000). In addition, ABPM offers the potential for improving both the evaluation and the management of identified hypertensive children (Alpert and Daniels, 1997; Khan et al., 2000; Sorof and Portman, 2000). The major unresolved question is: Does white-coat hypertension signal a tendency toward the development of hypertension later in life?

Finally, the issue of cost must be addressed. The expenditure for ABPM is considerably less than that for most diagnostic studies, but reimbursement is often unavailable.

EPIDEMIOLOGY

Surveys of BP patterns in children have sought to identify infants and children destined for hypertension in later life. Studies on neonates (deSwiet et al., 1980) and on children and adolescents from diverse backgrounds (Rosner et al., 2000; Sinaiko et al., 1999; Winkleby et al., 1999) have searched for significant abnormalities detectable early in childhood that can explain why some racial groups are at increased risk for cardiovascular disease. In particular, black children in the United States have been found to have increased cardiovascular reactivity induced by physical and psychosocial stressors (Anderson, 1989; Clark and Armstead, 2000; Treiber et al., 2000) and an increased sodium-lithium countertransport (Schieken, 1993), which could reflect an inherited defect in sodium metabolism (Alpert and Fox, 1993).

Among children in Finland, variations in the angiotensin-converting enzyme gene were associated with variations of BP in boys, but no associations with the angiotensinogen gene were noted (Taittonen et al., 1999).

In all groups, the most predictive indicator of sustained BP elevation is an antecedent elevated BP (Bao et al., 1995). Although an initial elevated recording during childhood may not evolve into later sustained elevation, Lauer et al. (1993) have shown that 24% of young adults whose pressures ever exceeded the ninetieth percentile as children had adult levels greater than the ninetieth percentile, a percentage that is 2.4 times that expected ($p < .001$). The predictability of adult BP elevations is strengthened considerably if elevated childhood BP levels are combined with childhood obesity (Grobbee, 1992; Lauer et al., 1993). If there is a positive family history for hypertension or obesity (defined as a BMI greater than the ninety-fifth percentile for age, gender, and race) or both, these abnormalities become even more significant (Lauer et al., 1993; Rosner et al., 1998).

Birth Weight and Blood Pressure

An association between birth weight and subsequent hypertension has been described. As noted in Chapter 3, the association is stronger in adults than it is among children and adolescents. Although agreement has not been reached (Falkner et al., 1998; Taittonen et al., 1996; Whincup et al., 1992), accumulated evidence indicates an inverse relationship between birth weight and BP (Hindmarsh and Brook, 1999; Yiu et al., 1999). Low-birth-weight infants had higher BP levels at 8 to 11 years (Taylor et al., 1997). That relationship becomes less strong during adolescence because of the changes imposed by somatic growth and sexual maturation. The trend, however, reestablishes itself during adulthood. The BP–birth weight relationship appears to arise from multiple intrauterine factors that interact with both genetic and postnatal environmental influences.

Tracking

The pattern of BP over time, referred to as *tracking*, has been examined in different age groups followed for varied periods of time in different settings. These studies have concluded that BP levels in children do track; however, the consistency of observations is greater for SBPs than for DBPs. Results of ABPM epidemiologic studies have reinforced and extended these observations (Barker et al., 2000; del Rosario et al., 1998). BP patterns have much greater stability the longer the follow-up, especially if the subjects are followed through adolescence (Bao et al., 1995; Donahue et al., 1994; Lauer et al., 1993). Longitudinal studies of children with BP patterns in the ninety-fifth percentile have revealed more consistent tracking when the patients are adolescents, obese, or the offspring of hypertensive parents or if echocardiographic changes that exhibit increased left ventricular mass (LVM) are present (deLeonardis et al., 1988; Hansen et al., 1992; Lauer et al., 1993).

Beyond the association with BP, changes in LVM have been related to growth (Janz et al., 2000; Schieken et al., 1998). LVM increased and tracked during puberty in concert with increments in somatic growth in subjects from the Muscatine study (Janz et al., 2000). The change in LVM does not by itself signify an increase in cardiac risk when considered for the pubertal years alone (Schieken et al., 1998). Daniels et al. (1998), in a study of 130 children with persistent BP exceeding the ninetieth percentile, found 14% to have LVM greater than the ninety-ninth percentile and 17% to have concentric left ventricular hypertrophy. When the data were expressed as the LVM index, 8% had an LVM index higher than 51, the cutoff associated with a fourfold increase in cardiovascular risk in adults (Daniels et al., 1998). Despite the difficulties of separating such pathology from the natural changes occurring during puberty, attention should be given to changes that may presage adult cardiovascular disease.

Factors That Determine Blood Pressure

Factors that correlate with BP levels during childhood, both cross-sectionally and over time, are being analyzed to identify which portend a subsequent rise in BP, with the hope that primary prevention of adult hypertension might become a realistic public health and clinical goal. Multiple factors have been reported to correlate with BP levels in children. In addition to those listed in Table 16-2, age (Lauer et al., 1993), gender (Daniels et al., 1996), and race (Daniels et al., 1996; Liu and Levinson, 1996) have been shown to relate to BP in children. Not only do white and black youngsters in the United States react differently to specific stimuli but, with maturation, higher BP levels are seen in U.S. blacks.

Genetic factors
Parental and sibling blood pressure levels (Mongeau, 1987; Schieken et al., 1993)
Increased salt sensitivity in U.S. blacks (Wilson et al., 1996)
Obesity (Klish, 1998)
Deletion of angiotensin-converting enzyme gene (Taittonen, 1999)
Environmental factors
Socioeconomic status (Winkleby et al., 1999)
Birth weight (Hindmarsh and Brook, 1999; Yiu et al., 1999)
Exercise (Alpert, 2000)
Mixed genetic and environmental factors
Height (Daniels et al., 1996)
Weight (Sinaiko et al., 1999)
Body mass (Freedman et al., 1999; Zhou et al., 2000)
Pulse rate (Zhou et al., 2000)
Somatic growth and sexual maturation (Daniels et al., 1996)
Sodium and other nutrient intakes (Falkner et al., 2000; Simons-Morton et al., 1997; Wilson et al., 1996)
Sympathetic nervous system reactivity (Urbina et al., 1998)
Stress (Clark and Armstead, 2000; Saab et al., 2001)

TABLE 16-2. *Epidemiologic factors related to blood pressure levels in children and adolescents*

The various factors listed in Table 16-2 are the major ones that correlate with BP levels in young people, the single best correlate being body mass. Data from the Montreal adoption study provided a statistical assessment of the contribution of various factors to the variability of BP in children (Mongeau, 1987) (Fig. 16-1). Most factors are either genetic or environmental, but some have features of both. Height, body mass, and muscular development depend not only on genetic influences but also on nutrition and exercise. Sodium intake may exert its effect on BP in those who are genetically predisposed to higher BP levels and are sodium-sensitive, especially U.S. blacks (Wilson et al., 1996). Obese adolescents have also demonstrated heightened responsiveness to sodium intake (Rocchini et al., 1989). An association between BP and increased sympathetic nervous system activity in whites and increased parasympathetic activity in U.S. blacks has been noted (Urbina et al., 1998). BP reactivity to some forms of stress reflects heightened vascular reactivity in children and adolescents with BPs that are higher and more labile (Saab et al., 2001).

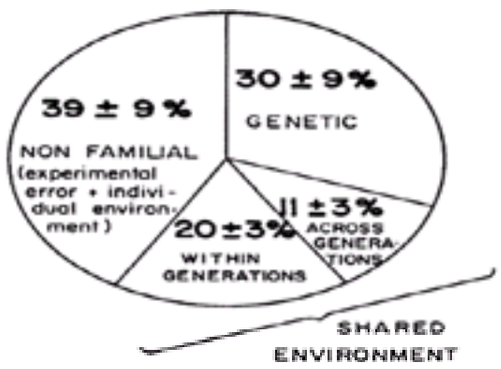

FIG. 16-1. The contribution of various factors to the variability of blood pressure in children. (Modified from Mongeau JG. Heredity and blood pressure in humans: an overview. Pediatr Nephrol 1987;1:69–75 .)

Genetic Factors

The influence of genetic factors on BP has been established by the findings of a correlation between BP levels of parents and their natural offspring (Mongeau, 1987; Taittonen et al., 1999; Wang et al., 1999), the lack of correlation between BP levels of parents and their adopted children (Mongeau, 1987), and comparisons of siblings (Wang et al., 1999) and twins (monozygotic and dizygotic) and their families (Schieken, 1993). Overall, the studies indicate that genetic factors play a strong role (Mongeau, 1987). Table 16-3 summarizes the differences reported among normotensive children with a positive family history versus those with a negative family history of hypertension.

↑ Carotid artery stiffness (Meaney et al., 1999)
↑ BP reactivity (Lemne, 1998)
↑ Leptin and insulin levels (Makris et al., 1999)
↑ Pulse and diastolic BP with dynamic exercise; ↑ pulse with isometric exercises (Mehta et al., 1996)
↑ Systolic BP in U.S. black male adolescents homozygous for the deletion polymorphism of the angiotensin-converting enzyme gene (Taittonen et al., 1999)
↑ Rate of sodium-lithium countertransport (McDonald et al., 1987)
↑ Sleep BP in U.S. black adolescents as measured with ambulatory BP monitoring (Harshfield et al., 1999)
Cardiac indices
↑ Intravascular septum–posterior wall mass index ratio (deLeonardis et al., 1998)
↑ Thickness of the interventricular septum during systole (Hansen et al., 1992)
↑ Left ventricular mass index (van Hooft et al., 1993)

BP, blood pressure; ↑, increased.

TABLE 16-3. *Characteristics of normotensives with a positive versus a negative family history of hypertension*

Environmental Factors

Of the environmental factors, increased body mass has increasingly been recognized as a major determinant of higher BP levels through-out childhood and adolescence.

Sodium and Nutrient Intake

The relationship between sodium and BP was comprehensively reviewed in Chapter 3. Simons-Morton et al. (1997) published a comprehensive review of the literature on diet and BP in children and adolescents. Despite methodologic problems, cited studies suggested that sodium intake is related to higher BP in children and adolescents, whereas data concerning potassium and calcium revealed no significant effect. Higher magnesium intake, however, has an inverse relationship with BP. Another study (Falkner et al., 2000), using folate as a surrogate for adequacy of micronutrient intake, concluded that black U.S. adolescents with higher folate and micronutrient intakes had a lower mean DBP. Until more data become available, current guidelines for caloric, fat, protein, and nutrient intakes should serve as a

foundation for prudent clinical practice and advice for children and their families (American Academy of Pediatrics Committee on Nutrition, 1998).

CARDIOVASCULAR RISK FACTORS

Obesity

As noted in Chapter 3, obesity has been identified as a major cardiovascular risk factor in adults. Similar observations have been made in children. The relevant pediatric data indicate that young obese individuals (BMI greater than the ninety-fifth percentile) have increased plasma insulin levels, increased lipoprotein levels, and increased BP levels, especially SBP (Sinaiko et al., 1999). The overwhelming evidence now supports the critical role of persistent obesity in youth as predisposing them to increased cardiovascular morbidity and mortality in adulthood. Berenson et al. (1995) reported the appearance of fatty aortic streaks at autopsy in young individuals with abnormal lipoprotein patterns coupled with elevated BP patterns. These factors combined with a lack of exercise set the stage for the development of progressive cardiovascular disease beginning in childhood.

Child care providers are therefore challenged to deal with a public health issue of increasing importance. The National Heart, Lung, and Blood Institute survey of primary care physicians indicates a significant gap in the application of accepted interventional measures for children at risk (Kimm et al., 1998). The challenge for child care providers is the creation of a feasible, proven strategy for intervention without inducing an unacceptable level of stress among vulnerable youngsters and their families (Klish, 1998; Sinaiko et al., 1999).

Target Organ Damage

Persistent BP levels in excess of the ninetieth percentile related to the height of the child are associated with target organ changes. Higher BP levels are associated with increased heart size and hemodynamic functional changes by electrocardiography, echocardiography, and Doppler ultrasonography (Kay et al., 2001). Autopsy studies also provide useful information (Berenson et al., 1995). Medial thickening of small renal arteries and intimal fibroplasia of coronary vessels are related to higher SBP levels. These observations provide evidence that hypertensive target organ damage already exists in childhood. In addition, microalbuminuria is associated with higher BP levels in black male Americans, consistent with the increased morbidity from hypertensive nephrosclerosis in the U.S. black population. The evidence of tracking and of target organ changes reemphasizes that the natural history of primary hypertension and hypertensive disease begins in childhood.

PREVENTION

Although no specific marker for the development of primary hypertension in young children has been identified, the roots of hypertension may be traced to early childhood. The evidence includes tracking for the highest deciles of pressure from childhood to diagnosed hypertension in later years, which is more pronounced in U.S. blacks (Berenson et al., 1996) and in the Japanese (Fukishige et al., 1995) than in other populations. Cardiac mass is increased in children with high-normal BP (Daniels et al., 1998). Detrimental exogenous factors that amplify the tendency toward higher or abnormal levels of pressure include adiposity or obesity or both (Yoshinaga et al., 1995), lack of exercise (Schlicker et al., 1994), excessive sodium intake in sodium-sensitive individuals (Wilson et al., 1996), tobacco or alcohol use (Uchiyama, 1994), and exposure to drugs with pressor or nephrotoxic properties (Clyburn and DiPette, 1995).

Individuals working with children and their families are in an ideal position to introduce preventive measures that will provide optimal cardiovascular health (Moller et al., 1993). Children and their families need detailed information about optimal dietary intakes, with appropriate cultural orientation. Once the dietary needs for cholesterol for myelinization of the central nervous system have been met (typically by age 2 years), recommendations for a prudent intake of fat should be provided. Family meals are an ideal setting in which to create lifetime healthful food habits; however, the composition of meals must be similar for all family members, unless there are medical constraints. Similarly, family activities that include age-appropriate exercise are helpful. Families must be informed of the deleterious effects of pressor agents (including tobacco, street drugs, and nonsteroidal antiinflammatory drugs that are being advertised as substitutes for acetaminophen). With these proactive steps, the health of children will be improved. Whether hypertension will be prevented remains unknown.

PRIMARY HYPERTENSION

General Guidelines

Asymptomatic children and adolescents who have a single casual BP recording that exceeds the ninetieth percentile for SBP or DBP according to age-specific distributions of BP for boys and girls should have their BP remeasured within 3 months. A BP value exceeding the ninetieth percentile but below the ninety-fifth percentile may be regarded as normal if height is higher than the ninetieth percentile but as abnormal if associated with adiposity (NHBPEP, 1996). The likelihood of repeated measurements being elevated is small, unless the child is obese or has a hypertensive parent. In selected cases, ABPM may separate a casual elevated pressure from a significant clinical problem (Khan et al., 2000; Sorof et al., 2000). If an adolescent has had repeated high-decile recordings and is consistently overweight for height, chances of the BP remaining at a hypertensive level are greatly increased.

Increasingly, asymptomatic children and adolescents with elevated BP are being identified as having primary (essential) hypertension, even though conclusive information about the incidence and prevalence of primary hypertension in young people remains unknown.

Evaluation

History

The family history should include the presence of hypertension and its associations (obesity, dyslipidemia, and diabetes in first-degree relatives) and BP levels of siblings. Although the increasing use of nonsteroidal antiinflammatory drugs has not yet been associated with childhood hypertension, pediatricians should be aware of these drugs' known nephrotoxic effects. Attention should be focused on drug abuse, with an emphasis on street drugs known to elevate BP, such as amphetamines and cocaine.

Primary hypertension in childhood and adolescence is typically asymptomatic. The most frequent symptom is headache, usually without distinguishing features that separate it from other etiologies. In adolescent athletes, headaches may occur after strenuous exercise. Symptoms such as seizures, nosebleeds, dizziness, and syncope are rare. Their presence suggests that hypertension has been exacerbated by pressor agents (e.g., sympathomimetics) or by an emotional crisis, particularly in adolescents. Otherwise, these symptoms are more often a reflection of severe secondary hypertension.

Physical Examination

The physical examination is oriented toward clues for secondary causes of hypertension, such as decreased femoral pulses, abdominal bruits, and cushingoid stigmata (Table 16-4). In children, in contrast to adults, retinal arteriolar tortuosity, arteriovenous crossing, and increased arterial light reflex more likely reflect long-standing hypertension rather than atherosclerosis.

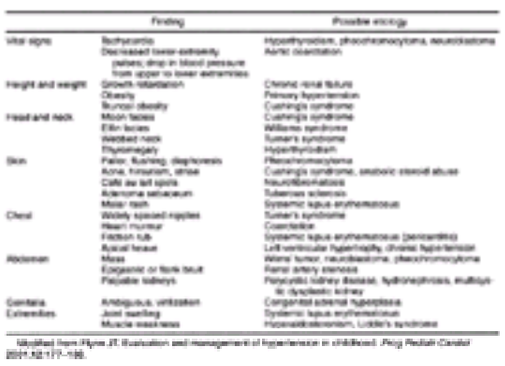

TABLE 16-4. *Physical examination findings in childhood hypertension*

Laboratory Studies

The likelihood that an asymptomatic child with persistently elevated BP will have a recognizable cause for the elevation is remote. In children with an identifiable cause for their hypertension, the history and physical examination usually reveal suggestive evidence of the cause, so that detailed diagnostic studies of children without suggestive evidence are not warranted. Only the screening laboratory studies shown in Table 16-5 are needed for most patients, but specific and specialized studies may be required in some (Flynn, 2001). Because echocardiography is the best means by which to detect increased left ventricular wall thickness or septal hypertrophy, it should be considered as part of the baseline evaluation, especially if pharmacologic intervention is required, so that reversal of abnormalities can be monitored and correlated with adequacy of BP control.

Phase	Studies
Screening tests	Urinalysis and culture
	Electrolytes, blood urea nitrogen, creatinine, glucose, calcium, phosphorus, uric acid
	Lipid panel (cholesterol, triglycerides)
	Complete blood cell count with differential, platelet count
Specific tests	24-Hour urine collection for protein, creatinine clearance, and electrolytes
	Urine and serum catecholamines
	Hormone levels (thyroid, adrenal)
Specialized studies	Echocardiography
	Renal ultrasonography
	Renin profiling (plasma renin and 24-h urinary sodium excretion)
	Renal ultrasonography with Doppler study of renal arteries
	Captopril renal scan
	Renal angiography with renal vein renins
	Magnetic resonance imaging
	Ambulatory blood pressure monitoring
	Renal biopsy

Modified from Flynn JT. Evaluation and management of hypertension in childhood. Prog Pediatr Cardiol 2001;12:177–188.

TABLE 16-5. *Laboratory evaluation of the child with hypertension*

Treatment

Treatment of primary hypertension is still empiric, because there are no long-term studies of either dietary intervention or drug therapy (Kay et al., 2001). In the absence of adequate data on safety and effectiveness of drug therapy, the decision as to whether a specific child should receive medication must be individualized.

Dietary Therapy

The first step in young children with persistently elevated levels of BP is a restriction of excess caloric and sodium intake. Short-term observations suggest that weight reduction in obese children and adolescents often normalizes elevated pressures (Rocchini et al., 1989). Sodium sensitivity may be greater in U.S. blacks, so that reduction of sodium intake may be particularly useful in those children. Diets rich in magnesium and micronutrients may be useful (Falkner et al., 2000; Simons-Morton and Obarzanek, 1997). Evidence concerning supplemental potassium and calcium is not persuasive, but a diet rich in fruits, vegetables, and fiber is prudent.

Older children and adolescents often eat in places other than their own homes. The ubiquitous presence of sodium creates difficulties for patients on a sodium-restricted diet in finding ways to choose appropriate foods when they are with their friends or away from home. An order of one superburger, French fries, and a chocolate shake contains approximately 1,100 calories and at least 1,000 mg sodium even without the addition of salt at the table. The physician and the adolescent patient must determine whether altering sodium intake poses a significant psychological burden. Dietary counseling coupled with self-monitoring of urinary sodium may prove effective if a limitation in dietary sodium is undertaken. The author has found that it takes up to 1 year for a child or adolescent to achieve a change in sodium appetite.

Drug Therapy

Treatment of asymptomatic, mildly hypertensive individuals requires confronting young people with the fact of illness, even though they do not feel sick. In particular, affected adolescents must cope with the notion of a long-term, unremitting illness that may foreshorten their life span if they do not comply. Treatment requires sensitivity to their special problems, including their desire to engage in active sports and, eventually, make career decisions.

Clinicians responsible for the management of children with hypertensive disorders not amenable to surgery remain handicapped by the absence of carefully controlled, short-term trials of medications for patients younger than 12 years and long-term studies of the effects of treatment on growth and development. Caution is advised about use of new agents that have not been adequately studied, with only retrospective or anecdotal data available on their effects in children (Bartosh and Aronson, 1999; Flynn, 2001).

Choices of Agents

As listed in Table 16-6, a wide array of agents with differing modes of action and differing side effects is now available. The highly regarded 1996 NHBPEP report recommends a stepped care approach, with initial therapy of diuretics or b-blockers. The most expedient approach is to choose a once-daily formulation with the fewest side effects. If BP control is not achieved, a second drug should be added. Often patients are taking other medications, and so children, families, and physicians must manage the many problems of polypharmacy. The goal of therapy is safe, effective BP control in a manner that is acceptable to the patient.

TABLE 16-6. *Antihypertensive agents useful for chronic treatment of childhood hypertension*

If either diuretics or b-blockers in sufficient dosage do not provide BP control, an angiotensinconverting enzyme inhibitor (ACEI) or calcium channel blocker (CCB) may be warranted. These agents have been used in children with renal hypertension and now are increasingly used in children with primary hypertension, because

they are well tolerated and have few apparent long-term metabolic side effects.

Angiotensin-Converting Enzyme Inhibitors

Captopril was the most frequently used ACEI in pediatric patients (Sinaiko, 1994), but longer-acting forms such as enalapril and lisinopril have supplanted it. Enalapril in doses up to 40 mg per day has been reported to be safe and effective in children (Miller, 2000; Soffer et al., 2000). Patients placed on an ACEI should be monitored for elevations in serum potassium and serum creatinine.

Calcium Channel Blockers

Short-acting nifedipine was the initial CCB used in pediatric patients and gained wide acceptance for acute hypertensive spikes in young children and adolescents (Blaszak et al., 2001). However, occasional acute hypotension with irreversible target organ damage has been associated with the use of the short-acting form in adults. As shown in Table 16-6, a new generation of CCBs is now available. The most commonly used agents are isradipine, amlodipine, and long-acting nifedipine. Isradipine has the advantage of an easily administered liquid form so that the dose can be titrated (Johnson et al., 1997). Pediatric experience is limited, and pharmacokinetic data are unavailable. Isradipine does not adversely affect myocardial function, and Strauser et al. (2000) reported that after 5 to 10 months of therapy for chronic hypertension, cardiac mass decreased. More recently, amlodipine, another dihydropyridine CCB, has been more widely used because of its safety and efficacy, ease of administration, and lack of adverse cardiac effects (Flynn, 2000c; Pfammatter et al., 1998; Tallian et al., 1999). Another advantage of amlodipine is the lack of significant interactions with commonly used drugs such as cimetidine and the nonsteroidal antiinflammatory agents (Tallian et al., 1999). Nonetheless, as with isradipine, long-term efficacy data are lacking for pediatric patients.

If adequate control is still not achieved with two or more drugs, the drugs may not have been taken or another diagnosis may be present, so that reevaluation is indicated, often with consultation.

Recommendations for Athletics

Asymptomatic children and adolescents with mildly elevated BP should be encouraged to participate in dynamic exercises. If they become symptomatic, they should be evaluated. Youngsters who are asymptomatic before, during, and after exercise should be allowed to play the sports of their choice. Sinaiko (1996) emphasizes the lack of evidence of an increase of cardiovascular risks among children with mild to moderate hypertension who participate in sports. Moreover, in a review of the literature on exercise and hypertension, Alpert (2000) reported an improvement, although not normalization, in both SBP and DBP with endurance training. However, for all symptomatic individuals, for all youngsters on treatment, and for those with electrocardiographic or echocardiographic changes of left ventricular hypertrophy, isometric exercises should be curtailed.

SECONDARY HYPERTENSION

The likelihood of a secondary cause of hypertension is much greater in prepubertal children than in adolescents. The most common cause of hypertension in prepubertal children is renal; coarctation of the aorta is the next most common cause (Sinaiko, 1996) (Table 16-7). The number of postpubertal children with renal hypertension varies with the setting. Adolescents with severe hypertension sent to a tertiary center for evaluation and treatment are most likely to have a renal basis, whereas those with mild hypertension seen in primary care settings are more likely to have primary hypertension. The number of pediatric patients with obscure causes for underlying hypertension is quite small. That fact should be kept in mind, so that expensive and invasive tests are reserved for individuals with significant symptomatic hypertension of unclear cause.

TABLE 16-7. *Identifiable causes of hypertension in children and adolescents*

Controversy persists about the need for and extent of investigation to exclude identifiable causes of hypertension. I believe that only limited laboratory evaluation is needed, but other investigators recommend more extensive studies (Dillon, 1987). Recently, a stepwise approach has been advocated (Bartosh and Aronson, 1998; Flynn, 2001). I believe the position taken by Sinaiko (1996) remains appropriate:

> One must recognize that the likelihood of identifying a secondary cause of hypertension is directly related to the level of blood pressure and inversely related to the age of the child. Severe elevations of blood pressure, regardless of age, warrant aggressive evaluations of blood pressure. However, since mild elevations of blood pressure (i.e., those slightly above the 95th percentile) are usually not associated with secondary disease, the initial evaluation is uncomplicated and aims mainly to identify renal disease.

Neonatal Hypertension

Neonatal hypertension is a particular problem among infants admitted to a neonatal intensive care unit. Neonatal hypertension has received increasing attention since the advent of Doppler ultrasonography for BP measurements, the introduction of umbilical artery catheterization, and extracorporeal membrane oxygenation; however, the incidence is estimated to be only 2% in those admitted to a neonatal intensive care unit (Flynn, 2000b). Moreover, most of these infants have acute hypertension that resolves as the underlying cause improves. Those requiring chronic treatment generally have underlying renal disorders (Table 16-8). The etiology for elevated BP covers a wide spectrum of conditions, many of which are acute and resolve after prompt intervention. The overriding priority in these severely affected neonates is to lower the BP safely and effectively. Treatment takes priority over diagnosis, which may safely be delayed until the newborn is stable and BP is under good control.

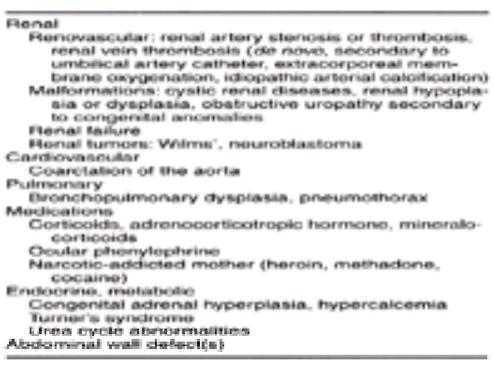

TABLE 16-8. *Major causes of neonatal hypertension*

Data regarding the use of antihypertensive agents in neonates are inadequate (Flynn, 2000b). Agents currently in use for acute, severe hypertension are listed in Table 16-9. The intravenous CCB nicardipine is increasingly being recommended because of ease of administration, safety, and efficacy (Flynn et al, 2001; Gouyon et al., 1997). Sodium nitroprusside has retained its role based on accumulated experience, tolerability, and few side effects with short-term use. Its major drawbacks are the need for intense monitoring and accumulation of toxic thiocyanate levels. The use of intravenous esmolol, a short-acting b-blocker, is largely con-fined to acutely ill, severely hypertensive infants who have undergone cardiovascular surgery. Flynn (2000b) indicates that caution is needed with the intravenous ACEI enalaprilat due to its potential for hypotensive effects with altered renal blood flow and resultant oliguric renal failure. The management of neonatal hypertension requires experience and knowledge regarding the special characteristics of these sick neonates in precarious circumstances.

Drug	Class	Dose	Route	Comments
Enalaprilat	Angiotensin-converting enzyme inhibitor	15 ± 5 μg/kg per dose Repeat q8–14h	Injection over 5–10 min	May cause prolonged hypotension and acute renal insufficiency
Esmolol	β-Blocker	Drip: 100–300 μg/kg/min	i.v. infusion	Very short-acting; constant infusion necessary
Furosemide	Diuretic	0.5 mg/kg/6–8 h	i.v. or p.o.	Often needed to avoid volume overload
Hydralazine	Vasodilator (arteriolar)	Bolus: 0.15–0.60 mg/kg per dose Drip: 0.75–5.00 μg/kg/min	i.v. bolus or infusion	Tachycardia frequent side effect; must administer with when given i.v. bolus
Labetalol	α- and β-Blocker	0.20–1.00 mg/kg per dose 0.25–3.00 μg/kg/h	i.v. bolus or constant infusion	Heart failure and bronchopulmonary dysplasia relative contraindications
Nicardipine	Calcium channel blocker	1–3 μg/kg/min	Constant infusion	May cause reflex tachycardia
Sodium nitroprusside	Vasodilator (arteriolar and venous)	0.5–10.0 μg/kg/min	Constant infusion	Thiocyanate toxicity possible with prolonged use or in renal failure

Modified from Flynn JT. Neonatal hypertension. Pediatr Nephrol 2000;14:302–341.

TABLE 16-9. *Intravenous agents for acute hypertension and hypertensive emergencies or urgencies*

Reflux Nephropathy

Vesicoureteric reflux is the term used to describe the retrograde flow of urine from the bladder into the ureter(s) and kidney(s). With severe reflux, the ureters become dilated and tortuous; the pelvocalycine outline becomes distorted by pelvic dilatation and, often, renal scarring coexists. This constellation of features, now known as *reflux nephropathy*, can be detected *in utero* by the use of maternal ultrasonography (Elder, 1992).

Reflux nephropathy is an antecedent of resistant hypertension and often leads to end-stage renal disease, regardless of medical and surgical intervention. The underlying renal lesion in this situation is typically focal segmental glomerulosclerosis.

Although the incidence and prevalence of reflux nephropathy are unknown, the condition is more common in girls. The diagnosis should be considered in any child with urinary tract infection, especially if the family history is positive for reflux nephropathy or if proteinuria is detected in a hypertensive child with a history of urinary tract infections and in the absence of fever. If reflux is detected, siblings should be screened with ultrasonography, because of the known familial incidence of this condition (Noe, 1992).

The decision about optimal management rests on the severity of reflux, analysis of renal function, and the family's ability to carry out long-term medical therapy. Early and severe scarring associated with high-grade reflux puts young children at significant risk whether or not they are treated medically or surgically by reimplantation. The International Reflux Study (1992) was a prospective, randomized 5-year trial comparing medical treatment with surgical intervention in 354 children. No differences between the two groups in renal growth or in the number or severity of renal scars were noted at follow-up.

HYPERTENSIVE EMERGENCIES

There are relatively few causes of hypertensive emergencies in pediatric patients (Table 16-10), and they are often easily diagnosed.

Renal
Acute glomerulonephritis
Chronic renal failure and end-stage renal disease
Hemolytic uremic syndrome
Reflux nephropathy
Renal artery stenosis
Systemic lupus erythematosus
Transplant rejection
Nonrenal
Coarctation of the aorta
Drug ingestion
Pheochromocytoma
Volume overload

TABLE 16-10. *Causes of hypertensive emergencies in pediatrics*

Treatment of hypertensive emergencies in young individuals has been made safer, easier, and more effective with the availability of agents listed in Table 16-9. The goal of treatment is a safe reduction of elevated pressure by decreasing both the SBP and DBP by approximately 25 mm Hg within the first 6 hours. Patients require constant monitoring in an intensive care unit. The preferred agents listed in Table 16-9 are intravenous nicardipine (Flynn et al., 2001; Michael et al., 1998), intravenous nitroprusside, and intravenous labetalol (Adelman et al., 2000).

CONCLUSION

Hypertension is an important pediatric problem. A focus on cardiovascular risk factors in children and their families, especially obesity, has become of paramount importance in the maintenance of lifelong good health. Diagnosis, evaluation, and therapy of hypertension in children can be provided in a sequential, costeffective, and psychologically protective fashion. The need for caution in the use of potent antihypertensive agents for neonates, children, and adolescents must be continually borne in mind. Recommendations in this chapter should assist the clinician in the management of hypertensive children and adolescents.

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