PREFACE

Hypertension Medicine is intended to be read by clinicians and to be helpful in a practical and immediate fashion. I have chosen topics that should cover common questions and emerging areas of interest. It always seems logical to explore in depth the basic sciences and epidemiology that provide the underpinnings of our knowledge of hypertension practice. But I have tried to avoid this temptation, using only the background necessary to explain or amplify clinical ideas.

We have emphasized brevity. I have asked our authors to minimize references and to prepare chapters short enough to be read comfortably at one sitting. We have sought an informal tone, as though the writer and the reader are having a collegial conversation. I have also asked the authors not to shy away from controversy or personal opinions; candor is vital when sharing clinical information and new concepts with colleagues.

The first section of *Hypertension Medicine* deals with the relevant background to hypertension: why we diagnose it, and why in most patients we now believe it should be treated aggressively. We then consider some of the major underlying mechanisms of hypertension, particularly those that help explain our approaches to treatment. The next section focuses on techniques for evaluating patients before treatment, bearing in mind that so many hypertensive patients have concomitant conditions like lipid disorders and diabetes mellitus, and often already have evidence of cardiovascular and renal changes. The final section deals with treatment. The discussion of antihypertensive drugs is relatively short. Rather, our major emphasis is in dealing with practical issues of management: how to select treatment to optimize results in difficult-to-treat hypertensive patients, and how to deal with major concomitant problems.

I am grateful to my many colleagues who were willing to share their expert knowledge and contribute chapters to this book. I also thank my distinguished friend Norman Hollenberg for agreeing to write a foreword, and my office coordinator Jeanne Minsky who worked so effectively with the authors and the dedicated editorial staff at Humana Press in bringing this project together.

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2 Effects of Aging on Blood Pressure

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High blood pressure (BP) (hypertension) is the leading cause of death by way of the cardiovascular consequences of heart attack and stroke. High BP is related in part to aging, especially in our industrial civilization. In certain "unacculturated" societies (such as that of the Yanamamo Indians) BP does not rise with age. People of this South American tribe are short-lived in general, and the lack of effects of aging on their BP may be related in part to their agrarian lifestyle and also the high potassium and low sodium diet of the hunter-gatherer.

DEMOGRAPHY

In the United States, the prevalence of patients with high BP increases every year, since half of the people over age 65 have hypertension *(1)*.

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Currently, 12–15% of the adult population is in the age >65 yr group, and 20% is ages 45–64 yr. The median age is at its highest point since the U.S. census began to track it more than 160 yr ago. One American in 8.7 is over age 65. There are more Americans older than 65 than there are ones younger than 25. By the year 2030, the age >65 yr group will double in number to one in four, or 65 million Americans. By the year 2040, 20% of the population will be over age 65, and another 20% will be in the age 45–64 group *(2).* Therefore, as the average age increases, and if the relationship of age with high BP continues, an increasing proportion of Americans will have hypertension. How important is this?

Hypertension contributes to the leading costs in health care. Currently, an American physician devotes 40% of his or her hospital time to adults above age 65. Ninety-seven percent of older adults use more than one drug per day, and 30% use more than five drugs per day. Hospitalized older adults receive an average of 10 different drugs. The expenses of senior care will consume 75% of the total health care dollar by the year 2030. Can the aging vascular disease relationship be altered?

The Framingham Study identified aging and high BP as the predominant risk factors for coronary heart disease. Although the hypertensive patient at age 30 has a very low risk of having a cardiovascular event, by age 65 his or her risk for stroke or heart attack will have increased fourfold over that of a person with normal BP. BP increases with age for both African Americans and Caucasians. Using the figure of 160/95 mmHg, the prevalence of hypertension over age 65 is 60% among African Americans and 44% among Caucasians. For 140/90 mmHg, 75% of African American patients and 60% of Caucasian patients have elevated BP.

SYSTOLIC HYPERTENSION

The prevalence of isolated systolic hypertension (>160 mmHg) increases with aging with 5% in the age 60–69 group, 10% in the age 70–79 group, and 16% in the age >80 group. The magnitude of systolic blood pressure (SBP) correlates even more closely with stroke, heart failure, coronary heart disease, left ventricular mass, and renal failure compared to diastolic blood pressure. Hypertension surpasses cigarette smoking, obesity, or family history and rivals cholesterol and diabetes as a risk factor for cardiovascular disease in the aging population. What are the changes associated with aging that lead to higher BP and increased cardiovascular risk?

False BP elevation is associated with aging as well. The so-called Osler maneuver is an evaluation of the peripheral pulse, which assists the physician in determining whether the resistance of the blood vessel walls is elevated compared to the pressure within the vessel. This resistance is related to the structural changes in the vessel wall with age. This maneuver palpates the radial pulse while the cuff occludes the artery in the upper arm. If the artery can be felt, it is said to be a positive test.

ALTERED CARDIOVASCULAR FUNCTIONS WITH AGE: CAUSES OF HYPERTENSION

Cardiovascular functions that change with aging, increased peripheral vascular resistance and arterial rigidity, are in concert with reduced cardiac output, cardiac and stroke index, baroreceptor sensitivity, and β-adrenoreceptor sensitivity *(3)*. Aging often affects renal function adversely and may lead to reductions in glomerular filtration rate, renal blood flow, and plasma renin activity, and these combined with increased plasma volume contribute to the rise in BP *(4)*. With aging there may be reductions in brain metabolism, nerve conduction velocity, basal metabolic rate, vital capacity, and maximal breathing capacity, which serve to raise BP. The effects of aging on the kidney are reductions in renal mass and renal tubular and arteriolar intimal function leading to elevated BP, along with increased glomerular sclerosis. Amazingly, perhaps, approximately one third of older patients have no loss of renal blood flow, renal mass, or creatinine clearance, whereas for most, there is a 30–50% reduction in renal cortical mass, blood flow, creatinine and free water clearance, and a heightened tendency to conserve sodium. Other physiologic changes occurring with aging have effects on BP regulation; the normal drop in BP after meals *(5)* (related in part to a shifting of blood flow to the splanchnic circulation) is more pronounced in the older patient. This may be related to baroreceptor hyporesponsiveness in some patients. Therefore, drugs taken at mealtime may result in more BP reduction than at other times because of the added orthostatic effects of eating.

Every year hypertension via aging leads to end-stage renal disease and enormous monetary costs, as well as suffering. In the 1990s, $2.8 billion was spent on the treatment of renal disease per year. Hypertension-induced nephrosclerosis accounts for 25% of end-stage renal disease in the United States, and African Americans are proportionately

at a higher risk of 4:1. What are some other pathologic alterations in the aging person that result in higher BP?

ALTERED ARTERIAL COMPLIANCE OF AGING: GENESIS

Along with the age-related reductions already discussed are several that reduce arterial compliance and enhance responsiveness to sympathetic neural stimuli *(6,7).* There is a tendency toward expanded plasma volume, although renovascular resistance is higher and renal blood flow is reduced. Simultaneously this results in lower plasma renin levels and cardiac output related to the increased vascular resistance. The aging process compromises sympathetic neural function; β-receptors are downregulated, and reflexively, perhaps, higher levels of α-mediated neural tone *(8)* increase peripheral vascular resistance and raise pulse pressure.

The compliance (the elastic recoil) of the great vessels is reduced with age and, in part, is a result of the elevated BP. Neurohumoral imbalance affects both the smooth muscle of the blood vessel and the impaired endothelium, and increased collagen is laid down replacing elastin. Along with increased apoptosis and cell death, the result is reduced arterial compliance. A surfeit of angiotensin II synthesis explains, in part, raised norepinephrine and endothelin release and concomitantly reduced release of prostacyclin and nitric oxide. Because of the drop in compliance, the reflected wave is heightened, the change in pressure after the initial peak or shoulder is enhanced, and systolic pressure rises and diastolic pressure lowers. The resultant heightened "pulse pressure" is predictive of both functional capacity of the patient in terms of the arterial blood flow reserve for exercising limb muscles and future cardiovascular morbid events *(9).*

ADDITIONAL MEDICAL CONCERNS IN SENIOR HYPERTENSIVE PATIENTS

Unfortunately, with aging there are concurrent ailments such as degenerative joint disease, diabetes mellitus, congestive heart failure, angina, and cerebrovascular disease, which further complicate the hypertensive process and its therapy in the aging patient. Atherosclerotic obstruction of the renal vessels may superimpose renovascular hypertension in the aging person. Therefore, it is necessary to examine the

senior patient carefully for renal and carotid bruits, and other vascular changes. The risks of cardiovascular complications—fatal and nonfatal coronary vascular events, strokes, renal disease, left ventricular hypertrophy, diminished cardiac output and arterial compliance, and increased peripheral vascular resistance—are all related to the rise in BP with aging. Thus, the prevalence of coronary heart diseases increases with age: of hypertensive patients >60 yr 44% have coronary artery disease, compared with 31% for those <40 yr. Concomitantly, the incidence of insulin resistance and type II diabetes increases with age. Some standard antihypertensives may interfere with the management of the diabetic patient. Thiazide diuretics and β-receptor blockers may affect glucose tolerance adversely, and β-blockers may mask the symptoms of hypoglycemia after insulin therapy.

THERAPEUTIC CONCERNS IN SENIOR HYPERTENSIVE PATIENTS

There are several important considerations in the pharmacokinetics of therapy in hypertensive seniors; drug clearance and thus half-life are prolonged. Drug absorption is generally unchanged, but distribution is altered secondarily to reduced body water and lean body mass, as well as to increased body fat. Hepatic elimination is reduced as liver mass declines, and thus so does metabolic clearance. Hepatic blood flow declines 40–45% by age 65, and liver microsomal enzyme activity is reduced.

β-Receptor blocker therapy may not be as effective as using diuretic or the low-dose combination of the two in the older hypertensive patient, perhaps owing to lower patient compliance because of real or imagined side effects. A minority of studies suggest that there is a reduction in the efficacy of angiotensin-converting enzyme inhibitor on BP control in the older patient, and others suggest that the calcium channel blockers are more effective in the older patient, especially those with low renin activity. Atenolol was not as effective as the calcium channel blocker verapamil in reducing both BP and left ventricular mass in a study of elderly patients with high BP.

Evidence from "outcome" trials of more than 20,000 elderly hypertensive patients demonstrated the benefits of BP control *(10).* The myth of "100 plus year age" as a marker for an acceptable SBP has been replaced by "less than 140 less than 90." These studies demonstrated that BP reductions of 12 mmHg systolic and 4–6 mmHg diastolic in seniors

are associated with reductions of coronary mortality of 25% and stroke mortality of 45% *(10,11)*. Thus, the relationship of aging to BP is a two-way street: rising BP may be fatal for the senior, and lowering it is potentially life saving. Patients should have BP lowered to the range of 130–140 systolic, and to 80–90 diastolic. In diabetic patients, the goal should be <85 diastolic, and <130 systolic *(12)*. Although BP rises with age, antihypertensive therapy has been shown to reduce morbidity and mortality significantly in patients older than age 80 as well as those younger than age 80. Current trends in treating hypertensive seniors breathe optimism. Fortunately, the proportion of hypertensive patients on therapy is increasing with age, with 47% on therapy in the age 65–74 group, compared with 41% in the age 55–64 group.

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