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Medical Management of Primary Hypertension

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PREFACE

HYPERTENSION is an extremely prevalent disease throughout the world and for much of its course is usually entirely asymptomatic. It has long been known that reduction of blood pressure with pharmacologic agents can alleviate symptoms and prolong life in those patients with the most severe forms of hypertension. Only recently have prospective population studies clearly implicated mild hypertension as an enormously important precursor of all forms of vascular disease. Still more recently, the beneficial effects of reducing blood pressure in mild to moderate hypertension have been demonstrated. Much still remains uncertain. However, enough evidence has accumulated to make it clear that more vigorous efforts than those now being made are needed to control blood pressure in many more patients.

This book summarizes a body of information concerning the value and objectives of treating primary hypertension and deals briefly with each of the drugs commercially available for this purpose. The range of material covered is by no means exhaustive. The differential diagnosis of hypertension and the patient workup are not dealt with at all. Any patient with hypertension should

be carefully studied to exclude renal parenchymal disease, renovascular disease, pheochromocytoma, aortic coarctation, primary hyperaldosteronism, and iatrogenic hypertension due to oral contraceptives. Most patients studied are found to have none of these disorders, and, by exclusion, a diagnosis of primary ("essential") hypertension is made.

The use of barbiturates and tranquilizers in the treatment of hypertension should be discouraged. Chlorpromazine and its congeners lower blood pressure in many subjects, but the effect is irregular and difficult to control. Use of the monoamine oxidase inhibitors is covered in this volume. Apart from these agents, there is no evidence that the commonly used tranquilizers are effective antihypertensive agents. Indeed, the tricyclic amines (imipramine, desipramine, and protriptyline) used as mood elevators can be extremely dangerous when given to patients with hypertension since they completely block the action of guanethidine and bethanidine and can result in dangerous rises in blood pressure when used in patients taking these drugs.

The antihypertensive agents described in this volume all act in one way or another on the cardiovascular system. With patience and perseverance on the part of the physician and with the patient's cooperation, a drug program can usually be evolved that will give satisfactory blood pressure control without intolerable side effects.

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THE RISK OF HYPERTENSION

THE great importance of blood pressure as a predictor of longevity has long been recognized by insurance companies. From actuarial studies done in the early years of the 20th century, it appeared that both high and low blood pressures were associated with an increased risk of dying. However, as death rates due to infectious disease diminished, the relation between blood pressure and mortality emerged in sharpened focus. The Build and Blood Pressure Study of the Society of Actuaries in 1959,[1] based on 3,900,000 policy holders and 102,000 deaths, showed that mortality ratios were more markedly affected by blood pressure than earlier studies had indicated. Not only is higher mortality predicted by even slight increases above the average in systolic and diastolic blood pressure, but the relation extends into the accepted normal range, with the lowest mortality ratios occurring with the lowest recorded blood pressures.

Any statement concerning the prevalence of hypertension depends on definition of the normal range of blood pressure, and such definitions have varied widely. Mortality statistics do not provide a reliable indication of prevalence since hypertension is greatly underre-

ported, even when known to the physician, and is seldom reported in atherosclerotic disease, to which it is a major contributor.[2] The National Health Survey of 1962 estimated that 26,000,000 people in the United States, or approximately 20 per cent of the adult population, had hypertension or hypertensive heart disease or both.[3,4]

Longitudinal population studies such as the Framingham[5,6] and Tecumseh[7] studies have more recently served to confirm both the high prevalence of hypertension and its great importance as a risk factor in cardiovascular disease. In the Framingham Study of 5127 men and women, 30 to 62 years of age, 18 per cent of men and 16 per cent of women were found to be hypertensive (defined as blood pressure greater than 160 systolic, 95 diastolic)[6] at the time of entry into the study. If "borderline" subjects (levels of 140 to 160 systolic, 90 to 95 diastolic) are included, 41 per cent of men and 48 per cent of women in this predominantly white middle-class population sample carry an increased risk because of elevated blood pressure. A higher prevalence and greater severity of hypertension occurs among nonwhite population groups.[8]

Before the advent of effective antihypertensive drugs, long-term follow-up studies of patients with hypertension demonstrated that the risk of cardiovascular disease and death is increased in direct proportion to the elevation of blood pressure and other indexes of severity such as retinal vascular lesions and cardiomegaly.[9-11] In malignant hypertension characterized by very high blood pressure and neuroretinopathy, a rapid reduction in renal function, with death due to uremia or cerebral hemorrhage, is characteristic of the untreated course,

male and female patients showing no difference in survival.[9,12] In less severe hypertension, the major risks are increased morbidity and mortality due to coronary heart disease and cerebrovascular accidents, both hemorrhagic and thrombotic. In all series, mortality figures show that women fare better than men.[6,13-17] This seems clearly to be related to the lower incidence and lesser severity of coronary heart disease among hypertensive (and normotensive) women.

A 14-year longitudinal study of the Framingham population shows that some manifestation of coronary heart disease develops in approximately twice as many men as women.[6] Although the absolute incidence and mortality is less among women, the relative risk of coronary heart disease with hypertension (or "borderline hypertension") is fully as great for women as for men, and may be somewhat greater in the older age groups.

A recent report shows hypertension to be the dominant precursor of congestive heart failure as it has developed in the Framingham population during 16 years of follow-up.[17a] Furthermore, congestive heart failure proved to be a lethal complication of hypertension, with only 50 per cent surviving five years after onset.

Cerebrovascular accidents are a proportionally greater cause of death and disability among women than men with hypertension, with thrombotic predominating over hemorrhagic accidents.[18] Fourteen-year follow-up study shows the risk of thrombotic stroke to be fully as great for women as for men, and directly related to the level of blood pressure. It is noteworthy that the risks of elevated blood pressure that emerged from the Framing-

ham Study were related solely to the blood pressure on entry into the study. Although the Framingham Study has not been concerned with the effects of therapy, reports of the biennial examinations have been transmitted to the physicians caring for the study subjects. These physicians instituted treatment whenever they deemed it necessary. Thus, if hypertension in these subjects has been modified by antihypertensive therapy in the intervening years, either treatment has been ineffective in reducing the incidence of vascular disease, or the risk of vascular disease has been underestimated by the study. A recent study of the records from four representative hospitals by Frohlich et al.[19] indicates that the presence of elevated blood pressure is frequently ignored by physicians caring for hospitalized patients. It is quite likely that ambulatory patients are often undertreated as well.

In a recent survey of industrial workers in Chicago[19a] 22,929 men and women were screened in 76 different plants. Prevalence of hypertension (blood pressure greater than 160 systolic, 95 diastolic) varied with age, sex and race. Of the entire group found to have hypertension, 59 per cent were previously undetected and untreated. Only 25 per cent were under any treatment, and only 11 per cent were under treatment and normotensive.

Systolic versus Diastolic Hypertension

The primary hemodynamic alteration in hypertension is a rise in peripheral resistance, causing an increase in

diastolic blood pressure. This change has been repeatedly documented in hypertensive patients.[20,21] The rise in systolic blood pressure that accompanies it is usually considered a secondary phenomenon. In most hypertensive patients cardiac output is normal or decreased. In some young patients, with greater than usual blood pressure lability, a primary increase in cardiac output occurs,[21,22] resulting in a predominant rise in systolic pressure. It has been postulated that this form of labile hypertension is a precursor of "true" hypertension, and follow-up studies in such subjects have shown some tendency for cardiac output to fall and peripheral resistance to rise with time.[23] Increased systolic pressure may also occur in high-output states such as anemia and thyrotoxicosis, and (most commonly) in the elderly, presumably owing to the loss of elasticity in the arterial tree. None of these conditions have been accorded the same pathogenetic potential as "true" or diastolic hypertension. With the exception of the high-output states, systolic hypertension and labile hypertension have generally been regarded as innocuous. Intimations that this view may be erroneous are evident in the data from the Build and Blood Pressure Study of 1959.[1] As pointed out by Gubner,[24] mortality increases progressively with each increment of systolic pressure, and this increase is evident at all levels of diastolic pressure, in both men and women in all age groups. Furthermore, the increment in mortality is related predominantly to cerebrovascular and coronary heart disease.

A recent report by the Framingham Study appears to confirm the importance of systolic hypertension as a risk

factor in cardiovascular disease.[25] Although systolic and diastolic blood pressures are highly correlated, multivariate analysis showed systolic pressure to be a stronger determinant for the risk of coronary heart disease than either diastolic or mean blood pressure in women, and in men over 45 years of age. It appeared to be independent of other variables, and to retain its importance when subjects with other risk factors for coronary disease were excluded from analysis. Diastolic blood pressure remained the stronger determinant only in younger men.

A study of isolated systolic hypertension in an elderly population followed for 48 months[26] demonstrated a significantly increased incidence of coronary heart disease, cerebrovascular accidents and overall mortality associated with elevation of systolic pressure. However, there was a substantially larger number of patients with diabetes in the group with systolic elevation, a finding also reported by Fineberg.[27] Kannel suggests[25] that systolic hypertension may accelerate atherogenesis, or may reflect an increased susceptibility to atherogenesis due to an altered state of the arterial wall. Alternatively, it may simply reflect advancing atherogenesis in the absence of other known risk factors. It seems evident that systolic hypertension merits more concerted study, and that it does not deserve the current cavalier attitude with which it is regarded.

Measurement of Blood Pressure

Little progress has been made in the technic for clinical measurement of blood pressure since the introduc-

tion of the sphygmomanometer by Riva-Rocci 70 years ago. The instrument is inherently inaccurate, giving an error of ± 8 mm of mercury for both systolic and diastolic pressure, even under ideal circumstances in normal persons.[28] Additional error is introduced by arrhythmia or tachypnea, large arm size, failure to position the cuff correctly, position of the arm, and unconscious digit selection by the observer. In addition to technical errors, variability results from ingestion of food, use of tobacco, bladder distention, climate variation, exertion, pain, the presence of the physician and the pressure of the cuff.[29,30] These changes are superimposed on moment-to-moment and diurnal variations. Some confusion still exists owing to the lack of uniformity with which physicians and nurses accept the "muffling" (phase IV) or disappearance (phase V) of the Korotkoff sounds as the diastolic criterion. Numerous studies have shown that phase IV occurs 7 to 10 mm above the direct intra-arterial diastolic pressure, and that under most circumstances, phase V corresponds closely with the diastolic pressure in the artery.[29,31] Nevertheless, the American Heart Association recommends phase IV as the best index of diastolic pressure, since "the laws of physics associate the point of muffling with diastolic pressure."[29] Also, in the presence of increased cardiac output, phase V may occur far below the diastolic pressure.

Some of the inaccuracies of the sphygmomanometer are inherent in the indirect method of measurement, but others could be reduced or obviated by improved design of the instrument. In spite of efforts to devise correction factors,[32] the errors in measurement due to

large arm size are unpredictable and nonlinear. It has been shown[33] that these errors can be largely eliminated and other random errors reduced by use of a bag that completely encircles the arm. Such a bag was recommended in 1959 by a committee of the World Health Organization.[34] The recommendation of the American Heart Association in 1967 states that "a bag 30 cm in length that nearly (or completely) encircles the limb obviates any misapplication."[29] In spite of these recommendations, the standard commercial cuffs contain bags 22 to 24 cm in length.

"Unconscious digit selection," the avoidance or selection of certain number values by the observer, is based on a tendency to sort subjects into "hypertensive" or "normotensive" categories, and has been especially troublesome in epidemiologic studies. This difficulty can be overcome with the use of devices that obscure or scramble the numerical values on the instrument,[35] and can be reduced by observer training.[36]

Twenty-four-hour records of blood pressure on normal subjects and patients with hypertension show a similar diurnal pattern in both groups.[30,37] A decline occurs during sleep to a constant level of blood pressure rising briskly in the morning in some and in others more gradually during the active hours of the day. In normal subjects the total diurnal variation averages 33 mm of mercury, systolic and 10 mm diastolic.[37] Larger total variations are seen in hypertensive subjects, although a decline similar to that observed in normal persons occurs during sleep, the low point varying with the height of the daytime pressure. During these studies the rise in

pressure occasioned by a physician's visit averaged 2 mm of mercury in normotensive subjects and 15 mm in patients with hypertension.[30]

In view of the shortcomings of blood-pressure measurement and the variables that influence it, it is surprising that the casual determination of blood pressure exhibits so clear a relation to the development of cardiovascular disease. Nevertheless, both the lowest and the highest of three variable readings have been found equally accurate as predictors of morbidity due to coronary heart disease.[38]