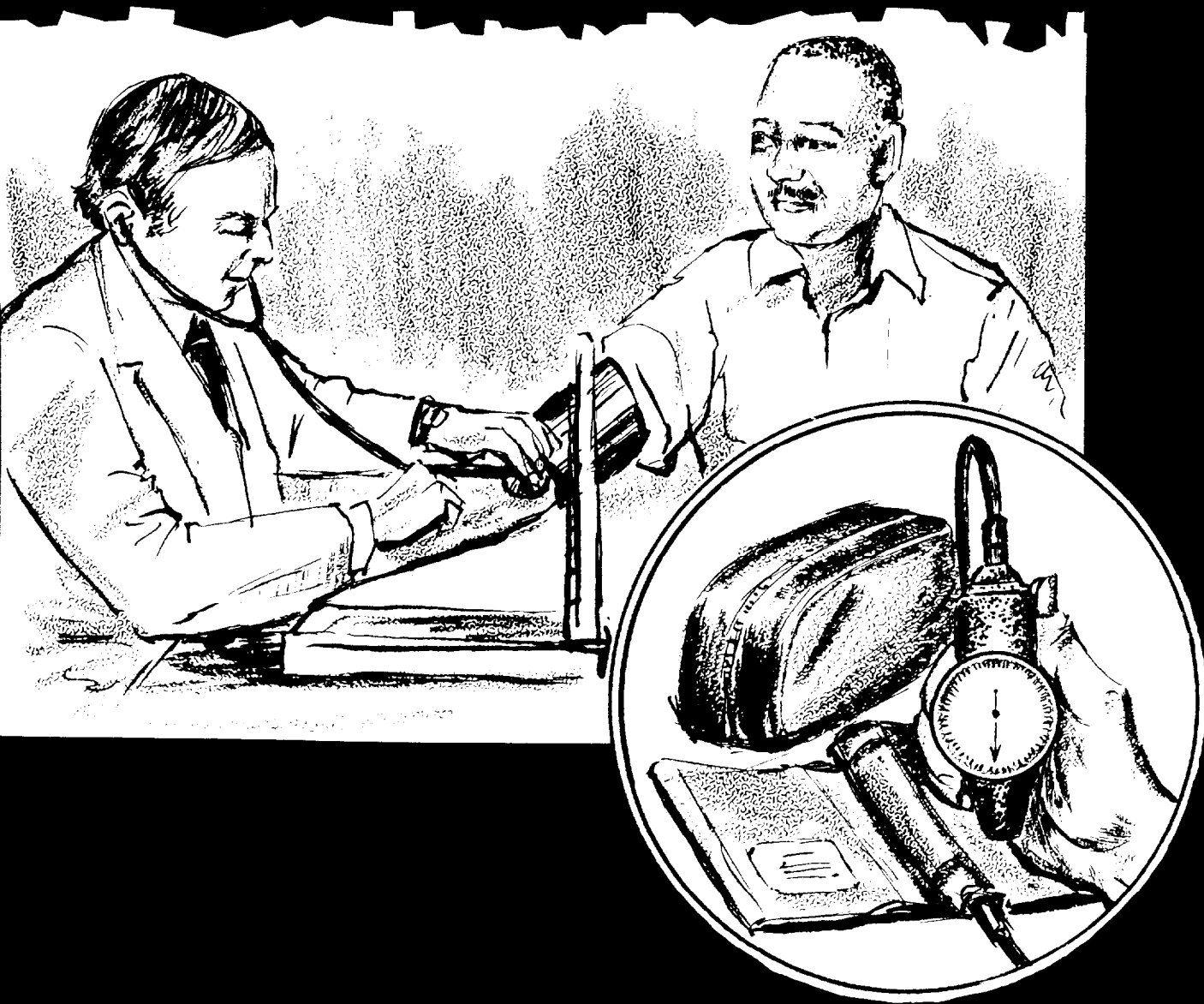


The Modern Management **OF HYPERTENSION**



VETERANS ADMINISTRATION - WASHINGTON, D.C. 20420 - JANUARY 1973

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OF HYPERTENSION

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INTRODUCTION

The high prevalence of hypertension in our veteran population makes it a disease of major importance. Through our vast facilities for delivery of quality medical care, we can make an important contribution to the prevention of the major complications of hypertension in this country.

A number of surveys (1-3), some of them house-to-house in various sections of the country, and amongst different socio-economic groups, have indicated that only about 50 percent of hypertensives know that they have hypertension. Of this percentage, only half were receiving treatment at the time of the survey, and only roughly half of them were being adequately treated, that is, their blood pressures were being well controlled. The most recent survey amongst employees of large business concerns in Chicago found that only 11 percent of such patients were receiving effective treatment (3).

What are the reasons for this sad state of affairs? The major reason is that the bulk of physicians have remained unconvinced that the treatment of hypertension justifies the associated side effects, expense, and inconvenience. There also is a highly prevalent notion that hypertension does not require continuous surveillance or control. Patients with hypertension feel well until major complications develop. It is difficult to convince them that they need to take daily medications which may, for a time at least, make them feel less well than they were before. It takes the physician's time and effort to educate and motivate his patients, and his time is already heavily committed to more acute and pressing treatment problems.

EPIDEMIOLOGY

Hypertension is one of the most ubiquitous of diseases. The National Health Survey of 1962 (4) was representative and extensive enough to permit a fairly reliable estimate of the prevalence of hypertension in the United States. From these data we know that there are approximately 23 million persons in this country (roughly one in every 10) who have a systolic blood pressure of 150 or higher, or a diastolic of 95 mm. Hg. or higher. The physician in family practice, therefore, is constantly coming into contact with patients with hypertension. If all of them were carefully and continuously followed, a major portion of his time would be taken up with the treatment of patients with hypertension.

Medical tradition with respect to benign essential hypertension has been characterized by therapeutic nihilism. The word "benign" often was taken literally. It was not conceded that antihypertensive drug treatment could prevent the development of cardiovascular complications. Antihypertensive drugs were looked upon as only "symptomatic" treatment, since the cause of essential hypertension remains unknown. The drugs were considered to be nonspecific hypotensive agents. Traditional thinking in therapeutics, largely conditioned by the success of chemotherapeutic agents in the treatment of infectious diseases, has emphasized the "magic bullet" concept. Find the cause and this will lead you to a specific cure.

Unfortunately, the cause of essential hypertension is likely not to reside in a single biochemical defect which will be correctable by chemotherapy. The cause of essential hypertension is as mysterious as it ever was. In the early stages of the disease no detectable abnormalities can be found other than the elevated blood pressure. In fact, Pickering has advanced a strong argument that blood pressure in the population is a continuum. When the frequency distribution of the various blood pressure levels is plotted, a monophasic curve is formed, with a slight skew to the right, indicating the hypertensive population. If there was a separate disease—hypertension—one would expect to see evidence of two peaks in the distribution, the first being the normal population and the second, or the right hand side of the distribution curve, representing the hypertensive population. Since the curve is monophasic, Pickering feels there are no separate hypertensive and normotensive populations (5). In this sense,

hypertension is a disorder of regulation, and the point where normality leaves off and the disease hypertension begins, is wherever we choose to put it on the range of blood pressure values found in the general population.

Epidemiology of Hypertension

The consensus of longitudinal studies in population groups indicates that blood pressure rises with age (6). Miall and Lovell (7) found that the change is related to the blood pressure level in youth, the higher the initial pressure the greater the increase with age. These results were not corroborated, however, in the Framingham data (8), where the tendency for the blood pressure to rise with age was not correlated with the initial blood pressure level.

In cross-sectional population surveys, systolic pressure rises up to approximately age 50, and then appears to level off (9). This tends to agree with Perera's observations that diastolic hypertension generally appears in the thirties, and rarely does the onset begin after age 50. Blood pressure tends to be lower in females than in males, up to age 55, and then crosses over, becoming higher than in males.

Blacks have higher systolic and diastolic blood pressures, on the average, than do whites (9,10). The prevalence of enlarged hearts, as manifested by X-ray and electrocardiographic abnormalities, also was found to be higher in blacks, the National Health Survey of 1962, and the death rate from hypertension, particularly in the 30 to 50 year age group, is threefold higher in blacks than in whites (11). In fact, hypertension is the leading cause of death amongst blacks. It has been said that for every black patient who dies of sickle cell disease, at least 100 die from hypertension.

The effects of occupation and physical activity on the incidence of hypertension and of stress related to occupation, are controversial. The results of various surveys are contradictory. There does appear to be an inverse correlation, however, between level of education and hypertension, the lowest average blood pressures being found in the more highly educated population groups (12).

Both cross-sectional and longitudinal surveys have consistently demonstrated a correlation between body build and blood pressure (9,13). The heavier individuals tend to have the higher levels of blood pressures. Also, in longitudinal studies, gain in weight with age was directly related to increase in blood pressure. The converse also was true in the Framingham study (14), with lower pressures among those who lost weight. Such association, of course, does not prove cause and effect. Dahl found, contrary to popular medical opinion, that reduction of weight had no effect on reducing the blood pressure of hypertensive patients, unless the salt intake also was sharply restricted (15).

It has been well demonstrated, in susceptible strains of rats, that a high sodium intake will aggravate hypertension, and produce a greatly increased incidence of cardiovascular complications (16). In man, diets very low in sodium (under 200 mg. per day; such a diet imposes special salt-free bread, milk, and no addition of salt in cooking) will lower the blood pressure of hypertensive patients. However, diets less severely restricted in sodium have not been shown to exert an antihypertensive effect. The presently popular "treatment" for mild and moderate hypertension of telling the patient to "quit eating salt," or a limitation to 3 grams of salt daily, has no demonstrated antihypertensive efficacy. As an investigator working in the era prior to the advent of antihypertensive agents, I well remember that only the most rigid restriction of sodium intake had any effect on blood pressure.

The epidemiological data on salt intake and blood pressure are controversial. In a northeast maritime province of Japan where the salt intake approximates 30 gm. per day, the incidence of severe hypertension and stroke is said to be very high (17). While Dahl found a positive correlation between sodium intake and level of blood pressure (18), the other surveys failed to find such a relationship (19-20). While it is clear that excessive sodium intake aggravates hypertension in rats, it is not established that the same relationship holds in man, except in the presence of renal failure.

This author believes that the primary factor relating salt to hypertension is the extracellular volume, including the plasma volume. Sodium is important in hypertension because it is the major determinant of extracellular fluid volume. An excess of salt in the diet can be handled by the normal human kidney, without expanding the extracellular fluid volume. However, in renal failure, even a moderate sodium intake expands this space, and hypertension is aggravated. Conversely, when and only when, sodium is restricted in the diet to the point of

shrinking the ECF, will there be a significant fall in blood pressure in man. The experimental evidence supporting this view is too lengthy to go into in this paper, but it is also consistent with our current knowledge of the antihypertensive action of oral diuretics.

A positive correlation between cigarette smoking and level of blood pressure has not been demonstrated (9,19,20), despite the fact that the immediate effect of smoking is often to raise blood pressure and heart rate transiently. The same is true of psychological stresses which raise blood pressure acutely, as there is no evidence to indicate that the frequent repetition of such stresses can raise the general level of blood pressure or cause hypertension. Both cigarette smoking and psychic stress can be regarded as transient aggravating factors, and as such are probably best avoided by hypertensive patients. In addition, cigarette smoking aggravates atherosclerosis, and in combination with hypertension, greatly increases the risk of atherosclerotic complications, particularly coronary artery disease.

An interesting positive correlation has been observed between blood glucose and blood pressure, which is independent of the effects of age, body build, and race (21). This study confirms a clinical impression that diabetes mellitus and hypertension are often associated.

The National Health Survey found a surprisingly high prevalence of cardiomegaly, by chest X-ray or electrocardiogram, even with mildly elevated blood pressure (12). Long term followup of mildly hypertensive patients revealed that 50 to 80 percent developed enlarged hearts (22). Life insurance data indicate a 50 percent increase in mortality over a 20-year period, in male patients age 35-45 with casual systolic pressures of 140 and diastolics of 90 mm. Hg. (23). This risk increases to 100 percent when the initial blood pressure is 145/95, and to 200 percent when the pressure is 160/100.

Most studies have indicated that morbidity and mortality rates are about twice as high in men as in women (22,23). This is especially pertinent to our veteran population. While the natural history of hypertension is extremely variable in different patients and in the two sexes, Perera has estimated from his data that the average duration of life following the appearance of diastolic hypertension (> 89 mm. Hg.) is about 20 years.

PATHOLOGY AND PATHOGENESIS OF LESIONS

The characteristic lesions of hypertension are found in the arterioles, and the type of lesion varies with the severity of the hypertension. When the diastolic blood pressure is persistently elevated at levels of 130 to 150 mm. Hg., or higher, fibrinoid necrosis of the media of the arterioles is seen in the kidney, spleen, pancreas, and brain, including the retinal vessels. The subsequent softening of the wall results in passage of transudates ("cotton wool" exudates in the optic fundi) and hemorrhage, both into the wall and through the wall. The vessel may thrombose, particularly in the afferent arterioles of the kidney, resulting in ischemic necrosis of glomeruli. Both focal or generalized edema of the brain may occur, leading to the neurological manifestations associated with acute hypertensive encephalopathy.

Fibrinoid necrosis represents a reaction of the arteriolar smooth muscle to the presence of a severely elevated blood pressure. In experimental renal vascular hypertension produced by constricting one renal artery, fibrinoid necrosis develops in the opposite kidney which is exposed to the elevated blood pressure, whereas, in the kidney which is perfused by the lower blood pressure because of the constriction, such lesions are not found (24). Similar observations have been made in patients with renovascular hypertension due to disease in one of the main renal arteries. In experimental animals and probably in patients with malignant hypertension, fibrinoid necrosis is arrested when the blood pressure is reduced with antihypertensive agents (2,5). Thus, it is clear that fibrinoid necrosis is the result, rather than the cause, of malignant hypertension.

Fibrinoid necrosis may be caused by prolonged vasospasm. In rats with renovascular hypertension, Byrom viewed the meningeal arterioles through "plexiglass" windows inserted into the skull, (26). When the blood pressure became severely elevated, Byrom observed segmental spasm of the arterioles which was so marked that the lumina were almost entirely eliminated. When the clip on the renal artery was removed, the blood pressure fell and the spasm was relieved. It is easy to see that if such severe spasm is long sustained, necrosis of that segment could result.

While fibrinoid necrosis of the arterioles represents a reaction to severely elevated blood pressure, the response to a moderate but long sustained increase in blood pressure (diastolic 95 to 130) is hyalinosis and hyperplasia of the media of the small arteries and arterioles, and even of some medium sized arteries, such as the arcuate arteries of the kidney. The media of the vessels become greatly thickened (hypertrophy) by hyperplasia of the smooth muscle. An increase in hyaline also can be detected by special stains.

The thickening of the wall leads to progressive narrowing of the lumina of these small vessels. In the kidney, which requires a high blood flow, there is a gradual but progressive loss of functioning nephrons secondary to ischemia. This nephron loss produces a characteristic finely granular appearance of the cortical surface. This process of nephrosclerosis is manifested in both "benign" and malignant forms. When the diastolic blood pressure is very high, fibrinoid necrosis is predominant, and the pathological process is called malignant nephrosclerosis. When malignant hypertension evolves from a preceding essential hypertension, or in any situation in which it is superimposed on a chronic hypertensive process, a mixture of lesions is seen in the kidney, with both fibrinoid necrosis in some vessels and extensive and severe hyperplasia of other arterioles, as well as small and medium size arteries. In the renal arteriogram, the finer arborizations of the arterial circulation cannot be visualized because of the marked narrowing of the lumina of the arcuate arteries, the contrast material appearing to stop short of the cortex of the kidney. In so-called benign essential hypertension, with lower diastolic blood pressures, only hyalinosis and hyperplasia are seen, which is confined to the arterioles and small arteries.

The arteries of the brain are thin walled, with minimal medial coat. Under the stress of an elevated blood pressure, a segment of the wall may give way and develop an aneurysmal dilation. The resulting microaneurysms are commonly found in hypertensive patients above the age of 45. They increase in number with aging, in the presence of hypertension. The weakened wall may rupture, producing cerebral hemorrhage, or the aneurysm may thrombose. Microaneurysms are particularly prevalent in the internal capsule, where cerebral hemorrhage or thrombosis occurs most frequently.

The aorta and large central arteries dilate in response to the increased wall stress produced by the hypertension. Eventually, the wall of the vessel loses its compliance and becomes a distended, stiff-walled tube. The area most affected by this stress is the proximal aorta, probably because its wall contains more elastic than smooth muscle tissue, and is therefore unable to resist the stress. The excessive distention of the proximal aorta probably pinches shut the nutrient small vessels entering from the adventitia. Therefore, in severe hypertension, necrosis of the media of the proximal aorta may occur and may be followed by a tear, resulting in dissection along the plane of the media; a dissecting aneurysm.

It is well known that hypertension and atherosclerosis often are associated. Although they represent two separate disease entities, it is apparent that the presence of hypertension accelerates and aggravates the development of atherosclerosis (27). The mechanism by which this occurs has not been clarified. However, it seems likely that the damage produced by the hypertension makes the artery more susceptible to the formation of atherosclerotic plaques. Prolonged and excessive stretching of the wall of the large arteries produces fragmentation of the elastic fibers and an increase in hyaline connective tissue. The mucopolysaccharide content of the vessel wall also is said to be increased. Loss of wall compliance and the changes in wall structure may well result in an increased susceptibility to plaque formation.

There are many "experiments of nature" which demonstrate the causal relationship between the elevation of blood pressure, *per se*, and the development of atherosclerosis (27). In chronic, severe pulmonary hypertension, such as occurs with large interventricular septal defect, atherosclerosis develops in the pulmonary arteries, whereas, it never occurs in this system when the pulmonary blood pressure is normal. In the aorta, atherosclerosis usually is more severe in the abdominal portion, but with coarctation of the aorta, atherosclerosis predominates in the proximal aorta, that is, in the region of the elevated blood pressure. In the congenital anomaly in which one coronary artery is derived from the low pressure pulmonary circulation and the other from the much higher pressure systemic circulation, atherosclerosis is found only in the latter.

Even slight elevation of blood pressure is associated with increased atherosclerosis. Because of coronary artery involvement, there is an increased risk of myocardial infarction and "sudden death." Data obtained from the "Pooling Project," of the Council on Epidemiology of the American Heart Association, indicated that in the age group between 30 and 39 years of age, individuals with a casual diastolic blood pressure of 85-94 mm. Hg. have five times the risk of developing major coronary events, as compared to those with diastolics below 85 mm. Hg. The difference is not so great in older age groups, or in elevations of blood pressure to the 95-104 range.

However, above 104 mm. Hg., the risk of coronary events again increases steeply. These data indicate that even borderline hypertension in 30 to 40-year-olds carries a serious prognostic import.

Atherosclerosis of cerebral arteries is a major cause of stroke, particularly in elderly patients with mild and moderate hypertension. Microaneurysms probably are more important in the stroke, developing in the presence of moderately severe to severe hypertension. The incidence of stroke increases progressively with slight elevations of blood pressure, in all age groups. According to the Framingham Study, the incidence of stroke is more than one and one-half times higher with diastolic blood pressure levels of 90-94, as compared to diastolic levels of 80-84 in the age range between 45 and 64 years of age, and is about three times as high with diastolic levels of 100-104 mm. Hg.

Because of the great emphasis on coronary heart disease and stroke in recent years, it is generally overlooked that congestive heart failure is an important cause of disability and death, and that hypertension is by far the principle culprit in its pathogenesis. In the Framingham Study, hypertensives developed congestive heart failure *six times* more frequently than normotensives. Congestive heart failure was a lethal phenomenon in this population, with only 50 percent surviving beyond 5 years.

“CURABLE” HYPERTENSION

Entirely too much emphasis has been placed on the identification and treatment of curable forms of hypertension. The impact of extensive diagnostic work-up of patients for curable hypertension on reducing morbidity and mortality in the general hypertensive population has been minimal. Physicians working in large teaching centers study a referred and selected sample of the hypertensive population, which causes them to overestimate the actual prevalence of curable hypertension. It is important to note that secondary forms of hypertension, including renovascular hypertension, were not observed in the Framingham population. The true prevalence of curable hypertension in the total population of hypertensive patients probably is less than 5 percent, and may well be as small as 1 percent.

Another important consideration is that complete cure is by no means always obtained by surgical intervention, nor is the operative morbidity and mortality negligible. In renovascular hypertension particularly, it is not possible to predict either cure or freedom from serious post-operative complications. The most clear-cut benefits of surgery result from repair of coarctation of the aorta, if diagnosed early enough, and from removal of a solitary pheochromocytoma. The diagnosis of primary aldosteronism is difficult to establish, and 5-year cure from removal of an adenoma is still not clearly defined.

The routine application of an elaborate, time consuming and expensive work-up for curable forms of hypertension in every patient, is an example of poor medical judgement. The search for curable hypertension should be individualized, principally to patients below age 35, those above this age who fail to respond to medical treatment, those who have had a recent increase in the severity of their hypertension, or those who give a suggestive history of such events as paroxysmal hypertension.

Simple routine tests for curable hypertension include the chest X-ray, to disclose notching of the ribs, characteristic of coarctation of the aorta; serum potassium, to disclose the hypokalemia of primary aldosteronism (being sure that the sodium intake has *not* been restricted and no diuretics have been used); serum glucose, both to detect diabetes mellitus, and also because it is frequently elevated in pheochromocytoma. On the other hand, intravenous pyelography should not be considered as a routine procedure, and should be reserved for the special cases where a renal lesion is suspected.

Pheochromocytoma often can be suspected on the history and physical examination. There may be a history of frequent headaches, or palpitation, or excessive sweating, blanching or flushing, which may be paroxysmal in nature. The patients tend to be thin and rarely, if ever, are obese. They often give the appearance of being hyperthyroid, and may have a fine tremor.

Cushing's syndrome displays the typical physical appearance of moon facies, central obesity, kyphosis and purplish abdominal striae, which should lead directly to the diagnosis. Primary aldosteronism has no characteristic clinical features, aside from muscle weakness and nocturia, which often are not present. However, it can be suspected by the presence of hypokalemia. Primary aldosteronism is still a rare disease, despite arguments to the

contrary, and is especially rare in our male veteran population. Normokalemic aldosteronism, as a cause of significant hypertension, or even as a valid disease entity, has not been definitively established. Therefore, if several serum potassium determinations are in the normal range, primary aldosteronism can be considered to be effectively ruled out, unless there is some other reason to suspect the presence of an aldosterone producing tumor.

Since the present practice, in patients above the age of 49, is to treat renovascular hypertension conservatively with antihypertensive drugs, a search for this condition in older patients is largely academic. It also is noteworthy that the condition is less common in males than in females, and is almost never found in black males. A great deal of needless laboratory investigation can be saved if patients are carefully selected for study. The rapid sequence intravenous pyelogram is the screening procedure of choice. Delayed excretion on one side, and especially the detection of a kidney that is more than 1 cm. smaller on one side than on the other, are the important points to consider. If available locally, the renal scan and renogram also are useful screening procedures. The renal scan is not very reliable in itself, often producing bizarre distributions of isotope within the kidney, but it is useful in locating the probes for the subsequent renogram. Positioning of the probes over the exact center of the kidneys is essential in obtaining valid renograms. Renal angiography and renal vein blood sampling for renin activity should be performed only in the patients who are suspected of having the disease on the basis of the above screening procedures, and in whom surgical rather than medical treatment would be indicated.

Unfortunately, medical tradition has grossly exaggerated the importance of detecting curable hypertension. For years, physicians have been taught that their major obligation was to rule out curable hypertension, and once this was done, their obligation to the patient had been discharged. The devastation of human lives that has resulted from this erroneous teaching can hardly be overestimated. The physician's responsibility only begins with the ruling out of curable hypertension, and he must not strain unduly his own or the patient's resources in doing so. The problem is to restore a perspective which is consonant with the relative worth of diagnostic and therapeutic procedures that are most apt to be effective in preventing the major complications of hypertension. The greatest cost-benefit ratio lies in the treatment, specifically in the drug treatment, of hypertension.

INDICATIONS FOR MEDICAL TREATMENT OF HYPERTENSION

The important factors which govern the degree of risk of developing cardiovascular complications of hypertension are the height of the blood pressure, the persistence of the elevation of blood pressure, the family history of hypertension and cardiovascular-renal complications secondary to it, and the degree of target-organ damage (fundus, brain, heart and kidney) already present.

The Height of the Blood Pressure

All epidemiological studies indicate that mortality is directly related to the height of either the systolic or diastolic blood pressure (10, 22, 23). Thus, life insurance experience indicates that in men age 35-44 years, the 20-year mortality rate increases 1.4 times the normal with a diastolic blood pressure of 90, and five times the normal with a diastolic of 100 mm. Hg. The increase in 20-year mortality in older patients with the same levels of blood pressure, while somewhat less than in the younger group, also is very great, in comparison to the normal population.

Many epidemiological studies are based on a reading of blood pressure taken at a single point in time. However, the course of the blood pressure over time may be highly variable. Some will exhibit a progressive increase, others will remain stable, while still others may revert to normal. While it is true that in a group of patients of age 38, with a diastolic blood pressure of 100 mm. Hg., the mortality is five times the normal, we cannot predict that any given individual in the group will have the same risk, since some live out a normal life span. Therefore, we need additional criteria, to assess risk and need for treatment in a given patient.

A number of studies indicate that borderline or labile hypertension is associated with less cardiovascular disease than is a persistent hypertension (28, 29). According to these studies, the risk of organic complications is three or more times higher in patients with persistent hypertension, than in patients whose blood pressure fluctuates above and below 90 mm. Hg. diastolic. A very elegant study was carried out by Sokolow and his associates, in which the blood pressure was measured several times each hour throughout the waking hours, by

the patient (29). The patient carried a tape recorder with him and wore the blood pressure apparatus beneath his coat. This study indicated that the persistence of hypertension was highly correlated with the presence of target organ damage, the patients with more labile pressures showing less damage.

All physicians are aware of the effect of emotions on blood pressure. The blood pressure taken in the absence of physical, mental or emotional stress, or apprehension, is called the basal blood pressure. It is not the lowest blood pressure that is recorded in the 24-hour period, since the latter generally occurs when the patient is asleep. The blood pressure taken as an isolated reading, or closely spaced series of readings, by a physician or nurse, is called the casual blood pressure. Casual blood pressure may be markedly different, or fairly close to the basal blood pressure in different patients. The degree of discrepancy between the two is not always predictable on the basis of the examiner's or the patient's appraisal of his emotional status. There is no reliable way of estimating basal blood pressure, except by determining it.

Basal blood pressure may be determined by any one of three methods, all of which are somewhat inconvenient. One method requires entering the patient into the hospital. He is not placed at bed rest, but rather is advised to be up and about the ward. The blood pressure is recorded four or five times daily for 4 days, and the readings of the last 2 days are averaged. Of course, the patient should not be faced with prolonged or discomforting diagnostic or therapeutic procedures during this period.

A second method, introduced by Dr. Smirk, is to have the blood pressure recorded for the better part of one day in a special clinic. Dr. Smirk had the blood pressure taken hourly by technicians, for an 8-hour day. However, with the availability of automatic machines such as the "Arteriosonde[®]" or similar instruments, if they are equipped with a digital printout, they can be set to record the blood pressure every 5 minutes, with the patient left alone in a quiet room. Under these conditions, it seems possible that a basal reading may be obtained after 2 or 3 hours. However, the minimum time to obtain a basal reading under these conditions has not yet been established.

The third method is to teach the patient, or a member of his family, to record the blood pressure at home. In employed patients, recordings usually are taken twice daily, in the morning and at night. A 2-week period usually is required. The readings taken during the last week are averaged (excluding sporadic readings greatly in excess of the average), in order to obtain an estimate of the basal blood pressure. A blood pressure apparatus can be given out on loan for the 2-week period. The patient and the individual taking the blood pressure at home should visit the clinic at the end of the first week, in order to check on the reliability of the readings. A stethoscope equipped with two sets of ear pieces (easily fabricated by using parts from a second stethoscope) is useful in conducting such a check.

The clearest indication for treatment is the presence of target organ damage. This, however, is not so reliably detected in the early stages of hypertension, since the changes are minimal. Normal individuals may show Grade I changes in the optic fundi, or have LVH by voltage criteria only, in the electrocardiogram. Clinical renal functional tests are insufficiently sensitive to pick up early mild damage to the kidney.

Hypertension, hypertensive cardiovascular complications and atherosclerotic complications, tend to run in families. If one parent of a patient had hypertension and died of a cardiovascular event, the patient's risk of developing cardiovascular complications in the future is great, if the hypertension is not controlled.

PATIENTS WHO SHOULD BE TREATED

The VA Cooperative Study clearly indicated that in male patients with diastolic blood pressures persistently at a level of 105 mm. Hg. or higher, the benefits of treatment were great, and that over a 5-year period the risk of developing morbid events was reduced by a ratio of more than 3 to 1 (30,31). In patients with persistent diastolic blood pressures averaging between 90 and 104 mm. Hg., the benefit of treatment was considerably less, with only slight differences favoring treatment. Furthermore, the complications of coronary artery disease were about the same in the two groups, and coronary artery disease is by far the most common complication in patients with diastolic blood pressures in the range of 90 to 104 mm. Hg.

On the other hand, this study indicated that serious toxic effects from the drugs used were uncommon, were easily recognized and easily remedied, by substituting another antihypertensive for the offending drug. Therefore, it seems justified to stretch the lower limit of diastolic blood pressure (for treatment purposes) to 100 mm. Hg.,

wherein the benefits of treatment would appear to definitely outweigh the risks. A lower limit of 100 mm. Hg. is set with the understanding that the value represents an average value obtained during at least two clinic visits other than the initial visit, and that an estimate of the basal blood pressure provides a reading of more than 89 mm. Hg. diastolic. Also, the assumption is made that the vast majority of patients seen in VA clinics will be males.

In patients with diastolic blood pressures averaging between 90 and 100 mm. Hg. on repeated visits, the benefit of treatment is still a matter of medical controversy. No doctrinaire statements can be made, because the decision to treat such patients must rest on opinion tempered by medical judgment. If the patient is below age 45, and there is a family history of hypertensive complications, or the presence of end-organ damage is evidenced in the optic fundi, EKG, urine, etc., then treatment probably is indicated. If the patient has neither a positive family history nor evidence of organic damage, little will be lost by a 1-year period of observation without treatment.

Given 100 patients with a diastolic blood pressure averaging between 90 and 100 mm. Hg., some will subside to normal over a period of a year, some will remain unchanged, and others will exhibit a progressive increase in blood pressure. The course of hypertension is so highly variable, that in the more borderline cases a protracted period of observation is needed to determine whether the elevation is persistent, progressive, or remittent. However, if a patient is not treated because of the spontaneous subsidence of the hypertension, annual followup still is indicated for a period of 3 to 5 years, to make certain that the remission is permanent.

CLINICAL PHARMACOLOGY OF THE PRINCIPAL ANTIHYPERTENSIVE AGENTS

The principal antihypertensive agents which are approved for use in this country are the thiazides and related diuretic agents, hydralazine, reserpine, alpha methyl dopa, and guanethidine. The diuretics act on the kidneys, hydralazine directly on arteriolar smooth muscle, and reserpine, alpha methyl dopa, and guanethidine on the sympathetic nervous system.

Thiazides and Related Diuretics

The principal action of these agents is to induce salt and water loss by affecting the renal tubular transport of sodium. Present evidence indicates that the principal site of action is distal to the proximal tubules. The urinary excretion of potassium also is increased.

When a thiazide diuretic is given to a hypertensive, but non-edematous patient, in continuing daily doses, the following sequence of events occurs: sodium, chloride, potassium, and water are excreted in excess for the first 2 or 3 days. The peak excretion occurs on the first day, and then gradually falls, so that after 3 or 4 days the excretion of sodium returns to the approximate pre-treatment level, and the excess diuresis stops, despite continued treatment (32).

Measurement of extracellular fluid volume before and after the diuresis indicates that the excess salt and water depletion during the first 2 to 3 days of treatment represents extracellular fluid loss. Roughly 1-2 liters of ECF are excreted, and present evidence indicates that the loss is more or less maintained for as long as the patient remains under treatment. The fluid loss is reflected in a decrease of body weight of several pounds. A portion of the ECF depletion is represented by the plasma volume, which is reduced by approximately 10 percent (33).

The blood pressure also falls during this initial period, suggesting that it is related to the diuresis, and possibly to the reductions in extracellular and plasma volumes. The important therapeutic implication is that a reduction of blood pressure does not occur unless there is a diuresis. The diuretic dose may vary somewhat in different individuals. For example, with hydrochlorothiazide, it may vary from 25 to 75 mg., but in patients with renal failure and greatly reduced glomerular filtration rate, hydrochlorothiazide is ineffective as a diuretic, even in large doses. Therefore, in such patients, agents with greater saluretic effectiveness, such as furosemide, must be used to obtain an antihypertensive effect. At the opposite end of the scale, some hypertensive patients, particularly elderly patients, are quite sensitive to even small reductions in extracellular and plasma volume; tolerable doses of hydrochlorothiazide in such individuals may be as small as 25 mg. once daily.

The effective dose of thiazide also will depend to some extent on the sodium intake. If a patient is adhering to a salt-restricted diet, a smaller dose may be required, than if he is ingesting liberal amounts of salt. In general, however, the dose of hydrochlorothiazide will be in the range of 25 to 50 mg. twice daily.

If the patient is ingesting liberal amounts of salt in the diet, and the doses of the diuretic are widely spaced, the patient may then fluctuate back and forth between depletion and re-expansion of the ECF. In some patients this may lead to considerable fluctuations of blood pressure from day to day. In general, patients with moderate to severe hypertension will require continuous diuretic coverage, at least during the initial 4 to 6 months of treatment, while patients with mild hypertension (or those with more severe forms who have been well controlled for long periods) may be able to maintain control of the hypertension with intermittent doses. If the latter pattern of dosage is used, however, it is important to check the blood pressure during the periods when there is no diuretic coverage.

The principal side effects of the thiazide diuretics are hypokalemia, hyperuricemia, hyperglycemia, or reduction in glucose tolerance, and sensitivity reactions, including skin rash and thrombocytopenic purpura.

Hypokalemia occurs in one-fourth to one-third of patients who are receiving continuous doses of thiazide diuretics (34). The hypokalemia is rarely severe, and serum potassium levels below 2.5 milli Eq/L are unusual during treatment with thiazides. The evidence is conflicting as to whether the hypokalemia reflects significant intracellular depletion of potassium, or represents only a reduction of extracellular concentration. There is no clear association between the hypokalemia and muscle weakness. Many patients complain of weakness and fatigue during the first few months of effective treatment with most of the antihypertensive drugs, but this is associated with bodily adjustment to the reduced blood pressure, rather than with hypokalemia, *per se*.

The principal risk associated with the hypokalemia resulting from thiazides is the resulting sensitization to digitalis-induced arrhythmias. The incidence of digitalis toxicity greatly increases in the presence of even minor reductions in serum potassium.

In addition to hypokalemia, hyperuricemia occurs in a significant percentage of hypertensive patients. In the VA Cooperative Study the incidence of uric acid levels of 8 mg./100 ml. or higher, as compared to controls, was 15 percent. Thiazides inhibit the tubular secretion of uric acid. This effect is greater at low than high doses and, in fact, thiazides are uricosuric at doses above the therapeutic level.

Despite the frequency of hyperuricemia, the incidence of gout is low, except in patients with a gouty diathesis, or in patients with renal failure. In both of these groups of patients, acute gouty arthritis often is precipitated soon after the patients are placed on thiazide diuretics. In other patients, it has not been demonstrated that thiazide-induced chronic hyperuricemia leads eventually to either gouty arthritis or gouty kidney.

In patients with essentially normal renal function, probenecid in doses of 0.5 gm. twice daily will normalize the serum uric acid level in thiazide treated patients. In patients with renal failure, a titrated dose of allopurinol will do the same.

In view of the above considerations, I will treat all patients with a prior history of gout, but who do not have azotemia with probenecid. If a patient with azotemia develops gout while under treatment with either thiazides or with furosemide, I will begin both colchicine and allopurinol simultaneously. The reason for the colchicine is both to treat the acute attack and to prevent its recurrence, which is very frequent during the first few weeks of treatment with allopurinol. To prevent flare-up in gout, colchicine can be given in a dose of 0.5 mg. once or twice daily. After the serum uric acid level has been stabilized at normal or near normal levels, I will discontinue the colchicine.

Thiazides reduce glucose tolerance, and they also will raise the fasting blood sugar (FBS) in some patients. In the VA trial, the excess prevalence of FBS values of 110 mg./100 ml. or higher, in thiazide treated patients, was 13 percent. The available evidence suggests that thiazides will induce diabetes only in "prediabetic" individuals.

A less frequent, but related, side effect of thiazides is the induction of an acute, severe hyperglycemia without ketosis. Fasting blood sugar values of 400 to 600 mg./100 ml. are seen with this reaction. The condition clears rapidly with discontinuation of the drug. It is sometimes possible to replace the original diuretic after the acute episode has subsided, with another chemically different diuretic, such as replacement of hydrochlorothiazide with chlorthalidone, or vice-versa.

Diabetes mellitus is very common in our middle aged and elderly veteran population. The appearance of mild diabetes in a thiazide treated patient does not necessarily mean that it was induced by the drug; nor is there any evidence to suggest that discontinuation of the thiazide will prevent the vascular disease that is associated with diabetes. If thiazides are necessary to obtain effective control of the blood pressure, I prefer to maintain this treatment, and simply treat the mild diabetes with diet. This decision is based on the evidence that reduction of blood sugar levels is of dubious effectiveness in preventing vascular disease in adult onset diabetes, whereas effective control of blood pressure is of great value in preventing the complications of hypertension.

Less common side effects of thiazide and related diuretics are related to sensitivity reactions, and include skin rash, particularly erythema multiforme and thrombocytopenic purpura. These reactions are rare, and often manageable by changing the diuretic from one chemical form to an unrelated one, such as was described for the management of the thiazide-induced acute, severe hyperglycemia.

Reserpine

Despite the fact that reserpine has been available for over 15 years, it is still the most misunderstood of all of the antihypertensive agents. Among the prevalent and false opinions, that are frequently expressed, are that reserpine is an ineffective antihypertensive agent, that it is too dangerous to use in man, that it is effective only in mild hypertension.

Reserpine generally is not effective unless it is combined with a thiazide. The U.S. Public Health Service controlled trial demonstrated that such a combination is as effective as thiazide plus alpha methyl dopa in controlling hypertension (35). However, reserpine is a double-edged sword. It has one very serious side effect, which is the induction of emotional depression. The experience has been, however, that such depression is much more frequently induced in patients who attain a high level of intellectual, economic and social accomplishment, and is unusual in patients who work primarily with their hands. Reserpine induces depression in individuals who are apt to react to emotional stress with an anxiety depression. There is some evidence to suggest that this response is due, in predisposed individuals, to depletion of catecholamines in the brain. However, in the great majority of patients who depend upon a clinic, rather than a private physician for their medical care, reserpine, in moderate doses, is a safe and often effective antihypertensive agent, when combined with a thiazide diuretic.

The reserpine-thiazide combination has some distinct advantages in clinical practice. The dosage schedules are simple and convenient. Thus, hydrochlorothiazide—reserpine, given in the commercially available fixed-dose combinations twice daily, is effective in the majority of patients who are responsive to any therapeutic doses of these medications. For even greater convenience, one can use a long acting saluretic agent such as chlorthalidone once daily, in the commercially available combination with reserpine (regroton). The less complex and the more convenient the regimen, the more apt one is to obtain the cooperation of the patient, and the less likelihood of confusion over doses, time of doses, etc., especially when a number of hypertensive drugs are being given in differing doses at different times of day. The thiazide-reserpine combinations also are reasonable in cost and, therefore, impose less of a strain on the budget of working people than do most other regimens.

The antihypertensive effect and the side effects of reserpine are due to its action in depleting catecholamines. The sympathetic nervous system still responds to stimulation, but somewhat more sluggishly, and the level of basal sympathetic tone appears to be reduced. The net effect is a blunting of sympathetic tone and of sympathetic pressor reflex responses, which combined with the central “tranquilizing” effect of reserpine, probably accounts for the antihypertensive action of the drug.

The partial depletion of catecholamines can be accomplished fairly rapidly with large (2 to 4 mg.) doses of reserpine parenterally, less rapidly with daily oral doses of 0.5 to 1.0 mg. orally, or slowly over a period of about 2 weeks, with daily doses of 0.2 to 0.3 mg. reserpine orally. Since there usually is no need for a rapid effect, the latter dosage schedule is preferable and simpler, in the usual setting of outpatient practice.

Depletion of catecholamines results in reduced sympathetic control and resulting parasympathetic dominance. In the heart, this leads to sinus bradycardia and diminished myocardial contractility. Another false concept concerning reserpine is that the reduced contractility will precipitate cardiac failure in hypertensive patients. There are several reasons why the reverse is true, that is, that reserpine given properly protects the patient against congestive heart failure. The first reason is that a fall of blood pressure reduces myocardial demand for oxygen by

greatly decreasing the work load on the left ventricle. The second reason is that the diuretic in the combination tablet prevents the development of fluid retention. Thus, the benefits of reduced afterload, and prevention of fluid retention greatly outweigh the disadvantages of reduced contractility.

Because of the increased vagal tone and bradycardia, reserpine treated patients may develop ventricular ectopic beats. This tendency is aided and abetted by the mild hypokalemia often induced by thiazides. However, the danger of ventricular ectopic beats has been greatly overemphasized. If the physician or the patient are concerned, one can substitute dyazide or aldactazide, thus avoiding hypokalemia, and give the reserpine separately.

Another discomforting effect of reserpine is nasal stuffiness. This is probably due to failure of vasoconstriction in the nasal mucosa. Nasal stuffiness generally is most troublesome at night, and some patients may require vasoconstrictive nose drops on retiring at night. Patients also should be told to discontinue reserpine during the acute coryzal phase of a cold, or if they develop epistaxis.

The vagal predominance leads to some increase in the secretion of gastric acid. However, in the usual therapeutic maintenance dose of 0.2 to 0.3 mg. daily, reserpine does not result in a significant increase in gastric acidity. Also, in the VA Cooperative Study, the incidence of peptic ulcer was only slightly and insignificantly higher in the reserpine treated, as compared to the control patients. While reserpine in large, parenterally administered doses, definitely increases gastric acidity, the risk with maintenance oral doses is negligible, and except for the presence of active or bleeding ulcer, need not contraindicate the use of this drug.

In addition to its potential ability to precipitate a severe depression, reserpine more commonly induces a so-called "tranquilizing" effect. The patient's drive for attainment may be replaced by lassitude, and ambition gives way to a more philosophical approach toward life. In patients who have the habit of superior attainment, particularly intellectual attainment, this reaction is decidedly unpleasant, and interferes with their normal way of life. However, in less motivated patients, the mood induced by reserpine is a pleasant one. The latter is especially true in those whose occupation and way of life requires fewer intellectual demands.

Fatigue is a related side effect, and it is often difficult to differentiate in deciding on its causation, between the emotional change induced by reserpine, and the loss of energy that often results when the blood pressure is lowered. If it is due to the latter, the patient should be reassured that the adjustment to a reduced blood pressure is a slow one, but that it will occur over a period of months, and that he will then recover from his present fatigue. If the fatigue is not so much physical as it is mental and emotional, the chances are that the patient is complaining of the mood changes induced by reserpine, and that some other regimen may be required.

Increased relative parasympathetic activity also can result in greater large intestinal motility, and resulting increased frequency of bowel movements. Increased gastric motility may lead to increased appetite. However, these are usually minor problems, in comparison with the importance of controlling the blood pressure.

Although reserpine is generally regarded as being ineffective in the treatment of severe hypertension, there are many exceptions to this rule. In outpatient practice, it is not at all uncommon to find that the addition of reserpine will control the blood pressure of patients who have seemingly been refractory to large doses of alpha methyl dopa, and/or guanethidine, plus thiazides. It is possible that the refractoriness was due to non-compliance, because of the complex dose schedules, or side effects associated with the more potent antihypertensive agents. Nevertheless, in the outpatient setting, reserpine-thiazide, plus hydralazine if needed, often is more effective than the more complicated and expensive regimens, even in severe hypertension. It is not possible to predict in advance who will respond to one regimen, as opposed to another. The successful therapist should keep an open mind on this subject, and maintain flexibility in his approach to management of the individual patient.

Alpha Methyl dopa

Possibly because this is the most recent of the antihypertensive agents, it is the most popular amongst house staff at many teaching hospitals. While it is a useful agent in many patients, its superior reputation for the long term control of patients who are not in renal failure, is undeserved. Approximately half of the patients treated with alpha methyl dopa respond well to it, if diuretic coverage is given, in addition. The majority of such patients seen in clinic practice would respond as well to reserpine, plus a thiazide (35).

The disadvantages of alpha methyldopa are that it must be taken three or four times daily, thereby placing a much greater demand on the compliance of the patient, that doses need to be individually adjusted, that it is relatively expensive, and that it also is not free of toxic effects or side reactions.

The advantages of alpha methyldopa are that it usually can be given without fear of inducing a depression, it seldom induces symptomatic orthostatic hypotension, and that occasional patients respond better to it than to other drugs. This again points up the need for individualizing each patient.

In general, I reserve alpha methyldopa for two classes of patients. One is the group of patients with essential hypertension who are not satisfactorily controlled on thiazide-reserpine, with or without hydralazine, and the other is patients with renal failure.

Alpha methyldopa is excreted in the urine; in patients with renal failure it appears to accumulate in the body. Thus, when one increases the dose during the titration procedure in patients with renal failure, one often overshoots the mark, because of renal retention of drug. Therefore, in treating the uremic patient, it often is necessary to reduce the dose of alpha methyldopa to a lower maintenance level, once an antihypertensive effect has been achieved. In addition to often being effective in reducing blood pressure in uremic patients (especially if fluid retention is controlled), alpha methyldopa does not decrease cardiac output or renal blood flow, and does not induce oliguria in such patients.

Although there has been much discussion of the action of alpha methyldopa as a "false transmitter," this attractive theory has not been established. The popular theory is that alpha methyldopa enters the metabolic chain of catecholamine synthesis, and eventually deposits in the sympathetic nerve endings as alpha methyl norepinephrine, replacing norepinephrine in the storage sites. However, alpha methyl norepinephrine appears to be as effective a pressor substance as epinephrine itself. In addition, there is evidence to believe that alpha methyldopa acts centrally, rather than peripherally at the sympathetic nerve endings. At present, it is fair to say that we do not fully understand the mode of action of alpha methyldopa.

The effective dose of alpha methyldopa must be individually determined in each patient, by a titration procedure. The range of effective doses varies from as little as 250 mg. to 2,250 mg. per day. Treatment can be initiated safely with a thiazide given separately, and with the beginning dose of alpha methyldopa at 250 mg. twice daily. This can be decreased to once daily, or increased to three times daily, depending on the response. Succeeding increases then are given as follows, as needed, and at as close to 8-hour intervals as possible.

AM	PM	Bedtime
250	250	250
500	250	500
500	500	500
750	500	750
750	750	750

The higher doses are somewhat inconvenient, and increases above this level are not worthwhile. Very few patients respond to a higher dose, who cannot be controlled by 500 mg. given three times daily. The common practice of prescribing four times daily doses is quite difficult for the patient to adhere to over long periods. Such a dose schedule is unrealistic, and invites poor compliance.

The most serious toxic effect reported with alpha methyldopa is hemolytic anemia. Fortunately, it is quite rare, although the induction of a positive direct Coomb's test is fairly common. A type of hypersensitization reaction has occurred during the first 6 weeks of treatment, which is expressed as a hepatitis characterized by low-grade fever and elevation of SGOT. This reaction seems to have become much less common in recent years, a change which is said to be due to improvement in the preparation of the drug. It should be remembered that ingestion of alpha methyldopa will cause a falsely positive test for catecholamines in the urine. However, since the drug does not enter the vanilylmandelic acid (VMA) route of metabolic degradation, the urinary VMA test for pheochromocytoma will not become positive.

The common side effects of alpha methyldopa are sleepiness and dry mouth. Patients who are engaged in sedentary occupations find the drowsiness to be particularly troublesome. They sometimes fall asleep at their

desk, or while watching TV. Patients who are physically active are not bothered by sleepiness. In many patients, the side effect tends to moderate with the passage of time. If dryness of the mouth is frequent or severe, it may be necessary to decrease the dose, or switch to another drug.

Impotence and depression have been implicated as side effects of alpha methyl dopa. However, it is my impression that the incidence is no higher than one would expect in an untreated population.

Guanethidine

This potent drug represents the big gun in the therapeutic armamentarium. It generally is reserved for the treatment of patients with moderate to severe hypertension who fail to respond to simpler, better tolerated regimens (36).

The limitations of guanethidine are basic to its mode of action. It produces a high degree of sympathetic blockade. This results in orthostatic hypotension. It often is difficult to control the blood pressure in the supine position with a dose that does not produce symptomatic orthostatic hypotension. The therapist usually is obliged to compromise at a dose which only partially reduces the blood pressure in the lying and standing positions. However, this partial reduction is vastly better than no control of the blood pressure.

Orthostatic hypotension is greatly influenced by the extracellular fluid volume, and its influence on tissue pressure. There is a considerable diurnal shift in the distribution of the ECF. As the day progresses, a large percentage migrates to the lower extremities and abdomen, acting like a compression bandage and preventing orthostatic hypotension from occurring. At night the process is reversed. During the hours in the recumbent position the excess fluid leaves the dependent portions of the body, and in the legs tissue pressure falls. Consequently, on arising in the morning, tissue pressure is reduced in the lower extremities, and venous pooling occurs on assuming the erect position. The result is diminished venous return and decreased cardiac output, leading to orthostatic hypotension and faintness, even syncope.

Obviously, the diurnal fluctuations in orthostatic blood pressure will be reduced if the amount of migratory ECF can be minimized. This is accomplished by giving a thiazide diuretic prior to and during titration with guanethidine. By depleting extracellular fluid volume, thiazides also enhance the antihypertensive effectiveness of guanethidine. Most antihypertensive agents induce a retention of salt and water, and this in turn causes an increased resistance to the antihypertensive effect of the given drug. The development of drug resistance due to this cause is prevented by an effective diuretic. This represents an additional reason why diuretics should be used in conjunction with guanethidine, as well as with most other antihypertensive drugs.

Guanethidine produces an effective block of sympathetic nerve endings. The parasympathetics are not affected and, as in the case of reserpine, there are side effects indicative of parasympathetic predominance. These include bradycardia and increased bowel motility. Oddly enough, nasal stuffiness is not evident. The effect on the bowel is to produce strong peristaltic rushes and more frequent bowel movements. This side effect is readily controlled with agents which inhibit the parasympathetic system, such as atropine or lomofil. No sensitivity reactions or direct toxic effects on body cells have been noted with guanethidine, the side effects all being a consequence of the sympathetic blocking action of the drug.

A feature of guanethidine which makes it difficult to use is the wide range of effective dosage in different individuals. In one patient, the effective dose may be as little as 10 mg. per day, and in another, 200 mg. Most patients respond to a dose of 25 to 50 mg. daily, but one cannot begin with such doses, because of the few who will develop orthostatic syncope. The action of the drug is long persisting, for at least 24 hours. Therefore, one dose per day is sufficient. In hospitalized patients, after background treatment is begun with an effective diuretic (in patients with renal failure this usually means furosemide or ethacrynic acid, while in others it means a thiazide), guanethidine may be initiated in a dose of 25 mg., since the patient is never far from his bedside, and the antihypertensive response in both the supine and erect positions can be recorded several times daily. The dose can be increased by 12.5 mg. daily (1/2 tablet), until an orthostatic fall in blood pressure becomes evident. Finer adjustment doses can then be made from this point, to achieve the optimal dose for that patient.

In outpatients, the titration procedure must be carried out with greater caution. The initial dose is 10 mg. daily, which can be increased at weekly intervals to 20, 35, 50, 75, 100, 150, and 200 mg., or until an

antihypertensive effect is obtained. In outpatients, the "post-exercise response" of the blood pressure is a more useful guide than simply taking the blood pressure in the erect position. At each visit, blood pressure should be measured in the supine position, one minute after standing, and immediately after the patient exercises by running or hopping in place until winded. The blood pressure is then measured while he is still standing erect, following the exercise. In patients receiving effective doses, there will be a significant fall in blood pressure following such exercise. If the post-exercise blood pressure is lowered, this is probably an indication that the patient is near or at the maximal tolerated dose, and that substitution or addition of other antihypertensive drugs is required.

With both inpatients and outpatients, the patient should be told about the orthostatic effects of the drug. During the titration period, he should be told to observe care on arising from the supine to the erect position, particularly after awakening in the morning. The patient should sit on the side of the bed for a minute before standing, to test for faintness. If such occurs, he should not attempt to stand, and should not take any more guanethidine until consulting the clinic. If he tolerates the dangling position, he can stand erect, but should wait beside the bed for a full minute before moving away. Patients frequently have fainted from orthostatic hypotension while standing to urinate, or while shaving. During the titration procedure, I advise patients to perform both functions in the sitting position. Quiet standing, rather than walking, is most apt to induce orthostatic syncope, because of loss of the pumping action of the leg muscles in aiding venous return.

Patients on guanethidine may develop retrograde ejaculation. This is due to failure of the sympathetics to activate a sphincter at the urethral-vesical junction, which normally closes during ejaculation. Aside from this change, sexual function is essentially unimpaired. However, failure to explain this side effect to male patients can result in needless concern, and loss of the patient's cooperation.

The effort to explain and minimize these various side effects that "can" occur with guanethidine may suggest that the drug is too troublesome to use. It should be emphasized, however, that most patients tolerate guanethidine with minimal side effects, when dosage adjustment is carefully managed.

Some patients who have been well controlled on guanethidine for long periods may suddenly appear to develop resistance to the drug. This may be due to poor adherence-the most common cause for drug resistance-or it may be due to undetectable fluid accumulation. If it is due to the latter, a large dose of furosemide will result in the reappearance of response to guanethidine. The test can be carried out by giving the patient 100 mg. furosemide intravenously, and then observing his blood pressure hourly in the clinic for the succeeding 4 hours. If the blood pressure falls, a larger dose or a change in diuretic may be indicated. Another reason for resistance is drug incompatibility. Imipramine and related compounds, for example, interfere with the penetration of guanethidine into the sympathetic nerve endings, and so block its antihypertensive effect.

Hydralazine

The action of hydralazine is unique amongst the currently available antihypertensive agents, in that it acts directly on arteriolar smooth muscle. Since the sympathetics are not affected by the drug, they will be activated reflexly by the fall in blood pressure to increase heart rate and contractility. Cardiac output rises, and the antihypertensive effect of the vasodilator is thereby partially nullified. In addition, the patient is often made uncomfortable by the increased cardiac activity, developing palpitation and dyspnea on slight exertion. Angina may be worsened. Therefore, hydralazine generally is given in conjunction with a sympathetic inhibiting agent, the most common being reserpine.

A further disadvantage of hydralazine is that it may induce fluid retention. In patients with cardiac complications, congestive heart failure may be precipitated. Therefore, all such patients should receive a diuretic in conjunction with hydralazine and a sympathetic inhibitor. Thus, hydralazine is usually considered as a third drug to be added to the regimen of patients who do not respond to thiazide-reserpine, thiazide-alpha methyl dopa, or thiazide-guanethidine. Thiazide and hydralazine, as a two-drug combination, may be effective and well tolerated in some patients with mild or moderate hypertension.

Vasodilatation of cerebral vessels after hydralazine medication can cause severe headache. Like the cardiac palpitation, headache is most prominent during the initial few days of treatment, and usually tends to abate, thereafter. To minimize its occurrence, and that of other acute side effects, I begin with a dose of 25 mg. twice daily, and increase to 25 mg. three times daily after several days or a week, then to 50 - 25 - 50, and finally to 50 - 50 - 50 mg. daily as the maximum dose.

Elevation of doses beyond 200 mg. may precipitate a hypersensitivity state resembling disseminated lupus. All manifestations of the latter, except the renal lesion, may occur, including skin rash, arthritis, pulmonary lesions, and the appearance of lupus cells in the blood. For this reason, high doses of hydralazine should be avoided.

Because of its vasodilating effect, hydralazine lowers peripheral vascular resistance more than any other currently available agent. As a result, there is a greater percentile fall in diastolic than in systolic blood pressure. The drug is particularly useful as an adjunctive medication when a partial antihypertensive effect has been achieved, and an additional reduction in diastolic blood pressure is desired.

Other Antihypertensive Agents

In my opinion, the other currently available agents are inferior to the five drugs described above.

Pargyline (eutonyl) is a monoamine oxidase inhibitor, and has both antihypertensive and antidepressant effects. It lowers blood pressure by sympathetic blockade, the mechanism of which is not clear. This results in an orthostatic hypotension. The drawback to the use of pargyline is that, in common with other monoamine oxidase inhibitors, it greatly potentiates the pressor effect of sympathomimetic amines. The latter require monoamine oxidase for their metabolic degradation, and when this enzyme is inhibited, the ingestion of sympathomimetic amines results in toxic concentrations in the tissues. Amphetamines, ephedrine, as well as tyramine contained in processed cheese, pickled herring, etc., if ingested, can result in severe pressor reactions. Imipramine and its analogues can produce vascular collapse in the presence of monoamine oxidase inhibition. There, also, are other serious drug incompatibilities, which makes the use of pargyline a form of therapeutic brinkmanship which, in my opinion, is unnecessary when other effective agents are available.

The ganglion blocking agents and the veratrum alkaloids have been replaced by the better tolerated newer agents already described. The dihydrogenated alkaloids of ergot share a similar fate because, when given orally, their antihypertensive effectiveness is poor. The same may be said for mebutamate (Capla), which appears to be little, if any, better than a placebo.

Investigational Drugs

There are several promising agents which have not yet been approved by the FDA. The most interesting is minoxidil (Upjohn). Like hydralazine, it is a vasodilator compound, but is much more effective as an antihypertensive agent, and has a longer duration of action, permitting twice daily doses for adequate 24-hour coverage. Like other vasodilators, it is most effective when combined with an agent which inhibits the sympathetic response to the heart, such as propranolol, reserpine, or guanethidine, and with a diuretic to prevent secondary fluid retention. Chidsey and his associates (37) have reported on the use of the drug in hypertension. My experience with it (in combination with other drugs) in patients with renal failure, and severe, resistant hypertension, has been dramatic. Several patients previously requiring chronic hemodialysis no longer require it, and control of blood pressure without orthostatic hypotension or other disturbing side effects has been most impressive. Because of a cardiac lesion observed in the dog following minoxidil, the investigative use of the drug has thus far been restricted to severe, resistant hypertension.

Bethanidine (Robins) is similar in action to guanethidine, but unlike the latter compound, it is short acting. It is being used extensively in Europe, particularly in England. The patient taking guanethidine often shows considerable diurnal fluctuations in blood pressure. This is due to the fluid shifts secondary to gravitational influence, as described in the section on that drug. Blood pressures are at their lowest point soon after arising, and become progressively elevated during the day, an effect which is only partially prevented by the use of diuretics. Because the action of bethanidine lasts only 6 to 8 hours, a smaller dose can be given on arising, and larger doses later in the day, to compensate for the diurnal variation in responsiveness. Bethanidine also is said to produce less effect on large bowel motility than guanethidine.

Propranolol (ineral) is being widely used in Europe in the treatment of mild to moderate hypertension. Why beta-blockade should be effective in reducing blood pressure is not clear, since the alpha receptors which supply the resistance vessels are not affected by the drug. Both bethanidine and propranolol are currently being evaluated in controlled trials by the VA Study Group on Antihypertensive Agents.

Diazoxide (hyperstat) is a parenterally effective vasodilator antihypertensive compound. It has been given in doses of 300 mg. intravenously, for the treatment of hypertensive crisis. This agent also produces hyperglycemia and sodium retention, the latter being controllable by the concurrent use of a diuretic. Experience with the agent has been favorable, as it is easy to administer as a single bolus injection, its action is prompt, and it does not produce vascular collapse.

Amiloride (Merck) is a potassium sparing diuretic which some investigators believe is more effective, or better tolerated, than the currently available triamterene and spironolactone.

PROGRAMS OF TREATMENT AND PRACTICAL DETAILS OF MANAGEMENT

Thiazide diuretics are the mainstay of treatment for all hypertensive patients, except those with renal failure, who cannot respond to these agents, and require the more potent diuretics. Thiazides control the hypertension in a large proportion of patients. In the others, thiazides will enhance the antihypertensive effectiveness of other drugs, which will be added later as needed. Therefore, in mild and moderate hypertension, it is customary to begin treatment with a thiazide, alone (38).

After 2 weeks of observation (weekly visits), if the hypertension is not controlled, the therapist may add either reserpine, alpha methyl dopa, or hydralazine, depending on the type of patient one is dealing with. For most patients, reserpine is the drug of choice, in a dose of 0.25 mg. twice daily for 2 weeks. If this regimen produces satisfactory control, the daily dose of reserpine should be reduced to 0.2 to 0.3 mg. daily, and a fixed-dose combination can be substituted, such as hydrochlorothiazide-reserpine twice daily, or chlorthalidone-reserpine (regroton) once daily.

If the patient has depressive tendencies, or responds poorly to reserpine, one can substitute alpha methyl dopa, but maintain the thiazide diuretic. When sedation is troublesome with both reserpine and alpha methyl dopa, which may be the case in some patients, the combination of a thiazide and hydralazine may be effective. This regimen is more likely to be successful in elderly patients, in whom baroreceptor reflexes are somewhat dulled due to aging, and in whom reflex increase in heart rate and contractility are reduced. The danger of inducing or increasing angina with this regimen in elderly patients has been over-emphasized. In fact, angina may be reduced in some patients.

The three-drug combination of a thiazide, reserpine, and hydralazine was used with great effectiveness in the VA Cooperative Study. It should be tried, however, only when the two-drug combinations of either thiazide-reserpine or thiazide-hydralazine have proven to be insufficiently effective. The three-drug combination is available in a single tablet as "Ser-ap-Es." The concentration of hydrochlorothiazide in this combination, however, is only 15 mg., which may be below the optimal level for many patients. In the VA trial, thiazide and reserpine (hydrochlorothiazide 50 mg. plus reserpine 0.1 mg.) were given in a fixed-dose combination, and hydralazine was then added as an independent tablet.

Hydralazine also may be added as a third drug in patients receiving thiazide-alpha methyl dopa or thiazide-guanethidine. It is unfortunate that hydralazine has been used primarily by some physicians in patients with renal impairment, because of the action of the drug in increasing renal blood flow. In my experience, hydralazine is least effective as an antihypertensive agent in patients with renal failure. Physicians who so limit the application of the drug, gain a distorted impression of its effectiveness.

Combination Therapy In Severe Hypertension Without Renal Failure

Many patients with severe hypertension, who do not have renal failure, will respond quite well to the three-drug regimen of thiazide-reserpine and hydralazine. A trial of this regimen is worthwhile because it requires little titration of doses, and usually is well tolerated.

Other regimens that may be tried in severe hypertension are thiazide plus alpha methyl dopa, or thiazide plus guanethidine. After titrating the dose to the optimal level, hydralazine may be added, if adequate control of blood pressure has not been obtained.

Treatment of Hypertension In The Presence Of Renal Failure

Patients with renal failure are resistant to long term treatment. It is difficult to maintain a reduction of ECF in such patients, and this represents an important factor in causing the drug resistance. If the patients are on a chronic hemodialysis program, their ECF will fluctuate markedly, falling after dialysis and rising between dialyses. Thus, they will be quite responsive immediately following dialysis and quite resistant immediately before the next dialysis. Patients who are receiving guanethidine may develop severe orthostatic hypotension, postdialysis, and severe hypertension, pre-dialysis.

The mainstays of background treatment in patients with renal failure are severe sodium restriction in the diet, and furosemide or ethacrynic acid. The doses of the latter must be large, sometimes as high as 200 to 400 mg. furosemide daily, preferably given as a single dose, to incite a diuresis in the damaged kidneys. Such intensive diuretic therapy results in further nitrogen retention and is, therefore, objected to by some nephrologists. The rise in BUN, however, reflects a hemodynamic alteration in the kidney, rather than further kidney damage. If the blood pressure is not lowered, further damage to the kidneys will result. Therefore, if an effective diuresis is needed to control the blood pressure, the rise in BUN is a small price to pay for such a benefit.

Patients who are treated this intensively must be watched for evidence of salt depletion. Rarely, one may encounter a patient who loses excessive salt through the kidneys, and becomes dehydrated and weak. This may be seen in patients with polycystic kidneys. More often, sodium depletion occurs when there is excessive sodium loss through the gastrointestinal tract. Excessive diarrhea or vomiting, or use of nasogastric suction, should alert the therapist to temporarily discontinue the diuretic, and to observe the patient for signs of sodium depletion.

In addition to paying particular attention to control of the ECF in patients with renal failure, one must always weigh the need for additional antihypertensive drugs. Of the available agents, alpha methyl dopa is generally the most effective.

Guanethidine also is frequently used, because of its effectiveness in reducing blood pressure. Because the orthostatic hypotension associated with guanethidine is so responsive to the volume of ECF, particular attention must be paid to maintaining a more or less constant reduction of the latter. Otherwise, the patients may fluctuate between disabling orthostatic hypotension and complete loss of antihypertensive response.

As stated in the section on new drugs, minoxidil, in combination with furosemide and either reserpine, alpha methyl dopa and guanethidine, has been outstandingly successful in managing the patient with severe hypertension and renal failure. Minoxidil should be added to the existing antihypertensive drug regimen in doses of 2.5 mg. twice daily, increasing to 10 mg. b.i.d., as needed.

THE PROBLEM OF COMPLIANCE

The greatest roadblock to the successful long-term treatment of hypertension is compliance. No matter how expert the physician may be in administering the antihypertensive agents, his efforts will fail if the patient does not cooperate. The most frequent cause for drug resistance is failure of the patient to adhere to the prescribed regimen. Almost invariably, patients will deny this fact, and experience has shown that they often are able to convince the therapist that they are complying. Physician judgment has been shown by pill counts and use of marker substances to be a poor guide as to whether patients are complying.

It is important that the physician understands the reasons for non-compliance. Studies that have been done on this important subject indicate the following:

1. The patient failed to understand directions.
2. The regimen was overly complicated.
3. The patient did not understand the nature of his illness and the need for continued treatment.
4. The patient was seen by too many different therapists. (Often the case in outpatient clinics).

5. The patient was made to feel like a second class citizen, because of prolonged waiting to be seen, prolonged waiting to receive his medications at the pharmacy, and by the busy, impersonal atmosphere of an overcrowded clinic.

6. Failure to care for intercurrent or associated illness.

Clinics for the long-term care of hypertensives must be specially organized and conducted with a view toward gaining improved compliance. Scheduling should be by appointment, in terms of exact time schedules. Waiting time should be minimal. If the patient appears at the scheduled time, he should be seen immediately. Arrangements must be made with the pharmacist to supply refills of drugs, without need for the patient to wait beyond a 10-minute period.

Since most of our VA clinics will use clinic assistants to see the patients on routine followup, the patient will be able to identify with a single therapist. It is important that the clinic assistant establish good rapport with the patient and evince an interest in him, not only as a patient, but also as a person. A feeling of mutual respect and trust should be developed between the therapist and patient. The clinic assistant should have time to listen to the patient's problems, both real and imagined, and should have at least a basic understanding of psychotherapy. This does not mean that the clinic assistant should offer psychotherapeutic advice, or become too emotionally involved in the patient's problems, but he or she should be a good listener.

Every patient who comes under long-term observation or treatment should have an indoctrination in the nature of hypertension, the relationship of hypertension to complications, and the rationale of preventive treatment. This may take the form of movies—such as the excellent movie of the American Heart Association called "What Goes Up," or of slide talks, pamphlets, or personal talks with the patient by the therapist. Such indoctrination should be repeated in modified form, from time to time, particularly during the first year of followup. Group discussion sessions also may be helpful. In such sessions, patients meet to talk about their reactions to treatment, what they understand the treatment is for, and problems they have encountered. It is important that the therapist determine whether the patient actually understands, and has not misinterpreted what has been said to him.

Patients expect care for all of their illnesses. They recognize the clinic as their health center. If they are turned away with the excuse that the clinic only will take care of their hypertension, their confidence and trust in the clinic will be seriously compromised.

The recording of the blood pressure in the home by the patient, or a member of his family, often is helpful to the patient in gaining a better insight into the action of the drug treatment. He will find out for himself that when the drugs are omitted the blood pressure will go up, and that moderate side effects may have to be tolerated in order to control the blood pressure. Another advantage is that the patient becomes a more active participant in the therapeutic process. Home blood pressure recordings should be reserved for the patients who are difficult treatment problems, and the equipment need not be loaned out for more than monthly periods.

Failure to comply also is due too frequently to side effects. Either the patient is embarrassed to discuss the side effect (as sometimes happens in the case of impotence), or he wants to please the therapist by making a good report. Some patients find it easier not to discuss reduction or omission of certain drugs, rather than to admit they did this because of side effects. They fear that the therapist will insist on their taking the drug, in any event.

It should be made clear to the patient at the outset of treatment that a variety of drugs are available, and that if one regimen is troublesome, another can be substituted. The therapist should evince an interest in determining whether the patient has had any side effects since he was last seen, and should attempt to draw out a history of real or imagined reactions to the drugs. If they are real, the regimen should be modified. If they are not drug related, the patient should be encouraged to try again, at the same time being given assurance that the reaction complained of was drug related.

It can be seen that gaining, and maintenance of, the compliance of the patient requires great skill, knowledge, tact, and a change in our present organization of outpatient clinics.

RECOMMENDED CRITERIA FOR TREATMENT

Average diastolic at disappearance (3 successive visits) over 104 mm Hg Treat all patients

Average diastolic at disappearance (3 successive visits) 90-104 mm Hg

Score 1 point for each of following:

- Age below 50
- Male sex
- Black
- All diastolics 95+
- Target organ damage (fundi, ECG etc.)
- Parent with major hypertensive complication

Average of Diastolics	Treat if Sum of Scores is
100-104	1 or more
95-99	2 or more
90-94	3 or more

CONCLUSION

Hypertension is currently the most important of the chronic cardiovascular disorders of man, because it is the one common cardiovascular disease in which treatment has been shown to be effective. An improvement in the quality of life and increase in life span is now possible of achievement for millions of Americans so afflicted. However, these benefits are not being delivered to the public effectively. The establishment of the VA Hypertension Clinics can serve as models for others to follow, in meeting this important problem.

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