When repeated blood pressure readings are greater than 150/100 mm Hg, a thorough investigation and examination of the patient should be made. However, this figure is an arbitrary one, for a blood pressure of 135/90 mm Hg in a 25-year-old human is abnormal and merits study and treatment. Although an elevated blood pressure may be labile, treatment is indicated, for these patients frequently develop a fixed elevated blood pressure.

Following the investigation, the patient should be told that modern treatment of high blood pressure is successful but complicated. Both of these factors increase as additional agents become available. He should be advised that the simpler medications will be prescribed initially. Return visits should be at two or three week intervals. If an adequate blood pressure decrease is achieved, the patient will be maintained on this regimen. If, however, the decrease is deemed insufficient by the physician, additional medication will be prescribed. Also, an increase in dosage may be made in certain variable dose drugs.

Moreover, it should be stated that high blood pressure can be merely controlled and not cured at present. Control requires continued drug administration and periodic visits, the frequency depending upon the judgment of the individual physician. In most instances, an office visit at four to six week intervals with a physical examination and evaluation of the renal and cardiac function at annual intervals is desirable. If the patient is told these facts prior to treatment, excellent cooperation usually follows.

The word “moderation” describes a desirable way of life for the hypertensive patient. He should be encouraged to be moderate in all phases of life. This includes tension, conduct of his business and home affairs, tobacco, stimulants, food, rest and recreation. If the patient is overweight a low calorie diet should be prescribed. Any deficiencies found in the routine physical examination and laboratory studies should be corrected whenever possible.

Although a restriction of sodium intake is of value, the salt intake must be less than 400 mg daily to be effective. Poor patient cooperation makes this difficult to achieve. Moreover, today’s diuretic agents have removed the need for constant striving to attain a very elusive goal.

The administration of sedatives and tranquilizers has only a mild lowering effect on blood pressure. Their value is chiefly in the apprehensive, labile hypertensive. A trial period is indicated with continuation following if the agent causes subjective or objective benefit.

The oral diuretics form the cornerstone of all therapy. The introduction of chlorothiazide more than ten years ago was a genuine breakthrough in the area of hypertension and a true application of a much too loosely used word. Many chemical modifications and new diuretics have been developed. However, other than greater potency requiring smaller amounts of the drug, similar results are obtained from the use of all the members of this group.

Chlorothiazide should be given in a dosage of 500 mg twice daily with the maximum effect occurring in two weeks. Approximately 50 to 60 per cent of the hypertensive patients seen by the average physician can be controlled adequately by the use of a diuretic (Fig 1).

Rare complications include skin rashes, pancreatitis, thrombocytopenia, leukopenia, glomerulonephritis and agranulocytosis. Azotemia may occur if renal function is impaired to the extent that the blood urea nitrogen is greater than 50 mg per 100 ml.
Hyperuricemia may occur with subsequent acute episodes of gout. Colchicine administration effectively controls these and the prophylactic use of probenecid (Benemid) .5 gm twice daily usually prevents additional attacks.

Elevated blood glucose and the development of mild diabetes occasionally occurs in those patients with predisposition to this disease. When indicated, a hypoglycemic agent may be given orally.

If routine serum potassium determinations are made, many will be found to decrease following diuretic administration. This is usually of some concern only when the patient is losing additional amounts of potassium by prolonged vomiting or diarrhea. A dietary intake high in potassium such as oranges, grapefruit, bananas or tomatoes may be adequate to correct this deficiency. If the patient is digitalized, has cirrhosis or is taking corticosteroids, daily supplementary potassium such as K Lyte (1 tablet twice daily) or Kaon Elixir (15 ml twice daily) should be prescribed.

If the desired decrease in blood pressure does not follow, one of the Rauwolfia group should be added. Some of the substances available include reserpine .25 mg twice daily, Rauwolfia 200 mg, alseroxylon fraction 4 mg (Rauwiloid) or syrosingopine 3 mg (Singoserp) daily. Very little difference in hypotensive effect exists following the administration of these different modifications. Some investigators have found somewhat fewer side effects with the use of the alseroxylon fraction and the whole root, but this is not striking. This group of agents requires about two weeks for maximum hypotensive effect and its addition to the diuretic will control 10 to 15 per cent more hypertensive patients.

Side effects include nasal stuffiness, drowsiness and insomnia followed by depression. Depression may be so severe as to precipitate a threat or attempt of suicide. However, these side effects are rare if the recommended dose is not exceeded. When they do occur, or if the blood pressure decrease is inadequate, the Rauwolfia compound should be omitted and the diuretic continued.

Methyldopa (Aldomet) is a much more potent substance than either of the two preceding groups. It should be added to the diuretic in a starting dose of 250 mg three times daily with a 250 mg increase at every office visit until a maximum of 3 gm daily has been prescribed or a satisfactory decrease in blood pressure obtained. Since a decrease in renal vascular resistance is caused by methyldopa, the use of this drug in those patients with an elevated blood urea nitrogen is particularly indicated. Proper dosage of this agent will cause the desired blood pressure control in an additional 20 to 25 per cent of all patients (Fig 2).

Untoward effects include mild drowsiness, drug fever and a positive Coomb's test. Drowsiness is usually temporary with beginning administration of the drug. However, doses greater than 1.5 gm daily may be accompanied by troublesome drowsiness. Drug fever is rare, while the frequently positive Coomb's test poses no problem and is not a reason for discontinuing the drug.

If the decrease of blood pressure is inadequate or side effects are intolerable, discontinue methyldopa. The diuretic should be given and one of the

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Rauwolfia group again prescribed unless severe side effects prevented its use. Rauwolfia decreases the dosage of hydralazine required and thus minimizes the side effects.

Hydralazine (Apresoline) is more potent than the Rauwolfia group and should be the next agent prescribed. The initial dose is 10 mg four times a day, increased after the first week to 25 mg four times a day. At weekly intervals increase the daily dose 25 mg until a total of 100 mg four times a day is being given, or an adequate blood pressure decrease has resulted. The maximum daily dose is 400 mg.

Hydralazine administration may lead to a clinical picture simulating acute systemic lupus erythematosus or an arthritis-like syndrome. Although this usually occurs only with doses greater than 400 mg a day, infrequent instances have been reported with a dose of 100 mg a day. Coronary artery disease and congestive heart failure are contraindications to the use of hydralazine.

If an insufficient blood pressure decrease occurs, guanethidine (Ismelin) may be added to the regimen of a diuretic, the Rauwolfia group and hydralazine. It should be given as a single morning dose of 10 mg, increased at weekly intervals by 10 mg until the desired blood pressure results in the standing position.

Side effects are diarrhea and failure of ejaculation. Frequent stools may be controlled with anticholinergic drugs (e.g. atropine).

The ganglioplegic drugs comprise the most potent group of antihypertensive agents, but are very rarely required today. Several agents are available, but mecamylamine (Inversine) is the one of choice due to its complete absorption from the gastrointestinal tract and more uniform effect. The dose is 2.5 mg twice daily increased by 2.5 mg at weekly intervals until the desired blood pressure is obtained with the patient in the standing position.

Side effects consist of constipation and dryness of the mouth and are parasympatholytic. This drug should be avoided if the blood urea nitrogen exceeds 50 mg per ml. The presence of coronary or cerebrovascular insufficiency merits caution in mecamylamine administration.

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The Mechanisms of Action of Antihypertensive Drugs

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The current treatment of essential hypertension is based on the following concepts: (1) a single cause has not been identified. Indeed, essential hypertension appears to be a multifactorial disorder. Specific therapy, therefore, is not possible;¹ (2) the homeostatic mechanisms that regulate blood pressure are intact in hypertensive subjects and responsive to physiologic and chemical interventions. This applies to baroreceptor activity,² sympathetic nerve activity³-⁴ and renin-aldosterone secretion.⁵-⁶ It is evident, however, that the baroreceptor “set” is abnormal in this disease because the high blood pressure is tolerated without invoking the hypotensive reflexes which are available.⁷-⁸ It is also evident that despite normal sympathetic nerve traffic, arteriolar tone is increased; the characteristic findings in essential hypertension are increased peripheral vascular resistance and a normal cardiac output.⁹-¹²,¹³ (3) it is the elevated blood pressure per se which is responsible for the clinical manifestations of hypertensive cardiovascular disease.¹⁴ Any consistent elevation of blood pressure, slight or marked, systolic or diastolic, is associated with increased morbidity and mortality.¹⁵ It is now clear that treatment can alter this picture. Deaths due to hypertension in the United States fell by over 50 percent between the “before” period of 1950 to 1953 and the drug therapy period of 1960 to 1963.¹⁶ Successful drug treatment may even lead to permanent remission.¹⁷ In a recent U. S. Veterans Administration cooperative study involving 143 hypertensive men, those treated with placebo suffered 27 severe complications and four deaths while an equal-sized and matched drug-treated group experienced only two severe complications and no deaths.¹⁸ (4) treatment, therefore, is required, and it is logical to attempt to lower blood pressure in hypertensive subjects by affecting regulatory mechanisms which may or may not be etiologically involved.

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