CLINICAL PROGRESS

The Management of Hypertensive Cardiovascular Disease

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A REMARKABLE variety of measures are effective in hypertensive disease including surgery, diet, drugs, and psychotherapy. Despite striking differences in their mechanism of action, these measures all have the ability to lower blood pressure. However, they are not simple to select and administer, nor are they successful in every case.

Except for rare instances, such as coarctation or pheochromocytoma, in which treatment can be directed at the specific cause of the hypertension, treatment remains empirical and largely a matter of trial and error. Nonetheless, such treatment is so effective in lowering blood pressure and alleviating many serious sequelae of hypertension that the outlook in hypertensive disease is more favorable than ever before.

The Advisability of Lowering Blood Pressure

The ease of measurement of arterial blood pressure has focused treatment and discussion, as well as the patient's anxiety, on the blood pressure level.

Objections to such treatment have included the beliefs that (1) it is the unaltered progression of vascular disease that kills and that lowering the blood pressure has no effect on this process and (2) lowering the blood pressure may actually be harmful by depriving the tissues, beyond the constricted arterioles, of adequate nourishment. Support for the former comes from such examples as the progression of coronary disease, despite blood pressure fall after sympathectomy.

When the blood pressure is lowered, however, a more typical picture is diminution of angina. The hypertensive patient with coronary disease or congestive failure whose blood pressure cannot be lowered is the one whose disease is likely to progress unfavorably. The second thesis, the occurrence of acute accidents such as myocardial infarcts or cerebral thrombosis after sudden severe hypotension, particularly from spinal anesthesia or ganglionic blockade, is understandable in view of the frequent coexistence of hypertension and vascular disease. This indicates the importance of lowering blood pressure cautiously and slowly in older patients and, when possible, with the least disturbance of important homeostatic mechanisms.

A strong brief for the role of persistent and marked blood pressure elevation in the pathogenesis of the vascular lesion of malignant hypertension is given by Pickering. Yet it is clear that there is no necessary correlation between the blood pressure level and the degree of hypertensive cardiovascular disease. Clinical improvement need not coincide with blood pressure fall. In animals, vascular lesions resembling those of malignant hypertension occur without high blood pressure and, in man, progressive papilledema has been described despite lowered blood pressure. These situations are exceptional, for most studies attempting to correlate blood pressure level and prognosis indicate that the higher the diastolic level the worse the long-range outlook. Probably the most compelling evidence for measures aimed at lowering blood pressure comes from the experience with malignant hypertension. In this condition, formerly almost uniformly fatal in months to a few years, drugs, diet,
surgery and fever have all induced remarkable remissions. The most recent data of Schroeder, Morrow and Perry\textsuperscript{6} indicate not only a high salvage rate, with restoration of vision and rehabilitation of many individuals back to work, but the virtual elimination of congestive heart failure as a cause of death in patients whose blood pressure is lowered adequately.

In less severe forms of hypertensive disease, satisfactory treatment requires more than alleviation of symptoms and lowering of blood pressure. Decrease in heart size, lessening or disappearance of albuminuria and improvement of electrocardiogram and retinopathy should follow. Proof that hypotensive measures prolong life in less severe stages of hypertension will be more difficult to obtain, but it seems logical that therapy, effective in the most severe forms of an illness, ought to have some value in milder forms. For all hypertensive patients, but particularly the less severe ones, the risks and discomforts of hypotensive therapy must be weighed against the life expectancy.

**Prognostic Factors**

Common clinical experience agrees with published reports\textsuperscript{7} that many hypertensive individuals live to advanced age and succumb to the same causes, mainly cancer, as persons with normal blood pressure. A “benign” course, that is, duration of life to within 3 or 4 years of the life expectancy, is indicated by 8 years of documented hypertention (at least 180/110), without evidence of cardiac, renal or severe fundal changes.\textsuperscript{8} However, a considerable number of hypertensive patients, including many with “benign” hypertension, die of congestive failure, myocardial infarction, cerebral hemorrhage and, occasionally, of uremia. When death or hemiplegia occurs from hypertensive disease, it is frequently at relatively young ages and often without much warning or overt evidence of vascular disease.

There is general consensus that “benign” disease is common in the female, especially beginning postmenopause and, conversely, the prognosis is poorer in males, especially young ones. The disease appears to be more severe and more difficult to treat in the Negro.

Determination of the prognosis for a single patient, except in the malignant phase, is difficult, even when early evidences of hypertensive disease, as grade II fundi, left ventricular hypertrophy or 1+ albuminuria, are present. Early morning headache may be present for many years without evidence of deterioration, but sudden onset of violent headache is an ominous symptom.

The blood pressure level, especially office readings, should be interpreted more leniently, particularly in view of revised (and higher) values\textsuperscript{9} of “normal” blood pressure with increasing age; but sustained high diastolic pressure, 130 or more, is an unfavorable sign. Office readings, especially casual ones, are notoriously poor guides to the level of hypertensive disease or to the effectiveness of therapy. As pointed out many years ago and repeated recently, home blood pressure readings are more reliable.

The prognosis for the individual must vary depending on the underlying disturbances (renal, endocrine, atherosclerosis, neurogenic, “essential”) that result in or are accompanied by hypertension. Subdivision of hypertension into types and in terms of response to specific hypotensive measures may eventually be helpful in this regard. Prognosis is certainly related to the family history as well as the presence and, more particularly, the rate of progression of vascular disease. An estimate of the latter requires prolonged observation. During this time, baseline studies are made, specific etiology for the hypertension is sought, good doctor-patient relationship established and, when indicated, hypotensive therapy is initiated. Examination of the eyes, the heart, and the kidneys reveals whether the patient is tolerating his elevated blood pressure with impunity. Hemorrhages and exudates in the fundi, an enlarging heart and progressive electrocardiographic changes of left ventricular hypertrophy and the appearance and persistence of albuminuria are indications that the process is not altogether benign. Difficulties in prognosis should not, however, result in allowing irreversible stages of the disease to develop while estimating the rate of progression.

As success in treating hypertensive disease...
increases, life expectancy for the individual will increase. This is already apparent in the improved outlook for malignant hypertension. Congestive failure, formerly a common cause of death in hypertension, is now so amenable to hypotensive therapy that death from this cause is quite infrequent. However, there is not yet clear evidence that cerebral thrombosis or hemorrhage is postponed or prevented.

Choice of Treatment

The multiplicity of therapeutic measures in hypertension indicates that none is ideal. However, each has specific indications and when properly used, often in combination, can modify many of the sequelae of hypertension. Current therapy includes: (1) psychotherapy, (2) diet, (3) drugs, and (4) surgery. Fever therapy is of historic interest only.

1. Psychotherapy

Much of the effect on symptoms and blood pressure level, formerly attributed to drugs, diet, and surgery, is due to the psychodynamics of the doctor-patient relationship. When this relationship is used wisely by the physician, it can become an important adjunct in therapy. In fact it is important even when the physician and patient are unaware of it. The patient must find stability, reassurance and protection in this relationship as well as a reorientation of his way of life. He must be taught to recognize the stresses that constrict his vessels and raise his blood pressure. He should be assured that his condition is benign and that casual blood pressure levels lack significance. He should be made to believe that he will not be paralyzed by a stroke—one of the most common and disabling fears of the hypertensive patient. He should be told that he has hypertension and that treatment is available, if necessary, but that frequently no specific treatment is required. For such assurance to be effective the physician himself must be free of anxiety about the disease and its treatment.

Some hypertensive patients have personality defects that antedate the development of persistent hypertension. These patients have a facade of affability and tolerance to situations, but actually they handle latent hostility poorly; they develop and sustain feelings of anger without expressing it. They have over-anxious reactions to real-life problems. Severe emotional stresses often coincide with the onset of hypertension or with acute episodes in the disease. Malignant hypertension commonly has its onset with severe emotional duress.

Psychiatric treatment directed at the personality defects and the individual's response to stresses is relatively new as a treatment in hypertensive disease. Some dramatic results in early hypertension and in a few cases of severe hypertensive disease are reported; but it is too soon to state whether intensive psychotherapy, even if practical, will be productive of maintained improvement in advanced hypertensive disease. In these patients, precious time should not be lost by relying completely on psychotherapy.

Superficial psychotherapy, firm reassurance, reorientation of the patient's life to avoid unnecessary stresses and common-sense hygiene are all that is required in many cases of high blood pressure, particularly early or labile hypertensive people without evidence of vascular disease. Mild sedatives (phenobarbital and bromide) are recommended, although there is no evidence that they exert a salutary effect on the prognosis. In some instances (see below), other drugs are advisable for the labile patient in addition to psychotherapy.

2. Diet

Dietary management for hypertensive disease should hold a more important place than it does in this pharmacetic heyday. Weight reduction for the obese patient should be carried out for its own sake, for its effect on general good health rather than expectation of normal blood pressure.

The mainstay of the dietary treatment in hypertension is sodium restriction. Of the various low-sodium diets the rice diet has the lowest sodium content (it is also the lowest in fat, cholesterol and protein). The claims of its original proponent concerning efficacy have been confirmed by others. Improvement may be expected in one fourth to one half of the patients treated. However, except in very
rigid or obsessive patients, adherence to the diet for prolonged periods is difficult. Demonstration of its effectiveness in restoring lost vision, for instance, will enable some patients to remain on the diet for long periods. For most individuals the greatest usefulness of the rice diet lies in creating ready acceptance of a 200-mg. sodium diet. As long as the sodium content is not raised above 500 mg. per day, the hypotensive effects are maintained even if fat and protein are added. There appears to be no advantage of the rice diet over a 200-mg. low-sodium diet. Because most low-sodium diets are low in protein, there is an initial loss of weight but eventual stability. For patients with heart failure or malignant hypertension, as well as uncomplicated hypertension, sodium restriction alone is often effective. In patients with cerebrovascular disease, it is undoubtedly the safest.

It is helpful to establish the patient’s response to salt restriction before instituting hypotensive drugs because low-sodium diets have an additive and possibly synergistic effect with some of these drugs. Certainly the hypotension resulting from ganglionic blockade is potentiated and it may be necessary to restore some salt to the diet to avoid excessive hypotension.

On this diet, even with initially normal kidney function, a low-sodium syndrome characterized by weakness, nausea, vomiting and collapse may develop in some patients. This is more likely in the presence of renal disease; yet some individuals with a moderate degree of nitrogen retention will show marked improvement on the rice diet. Curiously enough, the commonest complication noted on the rice diet was exacerbation of symptoms of peptic ulcer. As yet there are no reports involving combination treatment of low-sodium diet and Rauwolfia, but this ought to be a safe and effective program.

The rigors of sodium restriction make it obvious that it should be used only in patients with severe degrees of hypertension or with evidence of vascular disease such as grade III or IV eyegrounds, enlarged heart with congestive failure or coronary artery disease, or early renal disease. The only contraindication is a significant degree of renal failure.

3. Drugs

Although there are some criteria for the selection of particular hypotensive drugs, only a trial can demonstrate whether a given drug will be effective in a specific case.

A. Rauwolfia serpentina. The newest and most intriguing of the hypotensive drugs comes from R. serpentina. This ancient medicament from India was introduced into the United States by Wilkins\(^3\) a few years ago and has already had intensive trial and study.\(^4\) More recently it has been applied to a wide variety of psychiatric disorders. The crude root, standardized alkaloidal extracts and the pure alkaloid, reserpine, all seem to have similar pharmacologic properties, except that reserpine is about 100 times as potent as the crude root. An almost flat dose-response curve, unique among hypotensive drugs, gives reserpine a remarkable degree of safety. Children who have ingested very large amounts of the drug have suffered only from excessive sedation and diarrhea. Rauwolfia acts on the central nervous system, presumably at the hypothalamus and its ability to decrease blood pressure and heart rate has been attributed to a central inhibition of sympathetic (or an enhancement of parasympathetic) activity. The vasodilatation resulting in the blood pressure fall is mediated over sympathetic nerves to the vessels, apparently as a result of inhibition of reflex sympathetic vasoconstriction. However, postural hypotension does not occur except in very rare instances. Pupillary constriction is a characteristic effect in animals and nasal stuffiness in man. The latter may result in symptoms of a chronic cold, bloody nasal discharge and even sinusitis and otitis. Further evidence of parasympathomimetic activity is the increased secretion of hydrochloic acid in the stomach which could potentially exacerbate peptic ulcer; increased intestinal motility may result in diarrhea. In addition, Rauwolfia, like the Veratrum esters, interferes with certain reflex blood pressure rises, mediated by the central nervous system, that are the
normal response to anoxia or carotid sinus occlusion.*

Decreased motor activity in animals and placidity in man are effects that may indicate more complicated central nervous system action. The peculiar kind of sedation induced by reserpine has been aptly called “tranquility,” but this change in personality passes readily from calmness and quietude to languor and even true depression. The latter is more likely with excessive doses, but has also occurred with doses in the usual clinical range. Nightmares of a violent nature may occur but these are usually transitory. Decreased libido in the male is not uncommon. A few cases clinically like paralysis agitans have appeared under treatment with Rauwolfia, but these are apparently quite rare and usually related to excessive dosage. Emphasis on these side actions should not detract from the safety and remarkable therapeutic effects of these drugs. In general, Rauwolfia has only a moderate hypotensive activity and is said to be most successful in young, labile hypertensive persons without vascular disease. Yet often a marked and gratifying blood pressure fall is observed in elderly persons with “fixed” severe hypertension and definite evidence of hypertensive cardiovascular disease. The hypertensive personality described above is altered. The patients seem better able to withstand many emotional stimuli. Anxiety is diminished. The tachycardia, blood pressure rise and “diencephalic” facial flushing (with which some hypertensive women greet their doctor) or other stresses disappear under treatment with Rauwolfia. Many of the so-called neurotic symptoms such as dizziness, headache, nervousness and insomnia are relieved. Some blood pressure diminution is noted in about one half of the patients treated.

The dose range of reserpine is 0.1–1.0 mg. daily by mouth, the average being about 0.25–0.5 mg. The drug is best taken at night.

* Reserpine causes increased excretion of 5-hydroxy-indole acetic acid, a metabolite of serotonin, in dogs and the discharge of large amounts of serotonin from the small intestine of rabbits. Serotonin is capable of activating the coronary chemoreceptor reflex.18

Parenteral reserpine (1–2.5 mg. intravenously) has in general the same effect, predominantly sedation and a moderate blood pressure fall lasting about six hours. Neither tolerance nor addiction has been reported. Best effects may require one to several weeks of treatment; similarly, when the drug is omitted hypotensive effects may last for weeks. Undesirable side effects are often controlled by omitting the drug for 1 week in 4. If daytime sedation is excessive, the entire dose should be taken at night. Synergistic effects with other hypotensive drugs are always difficult to prove, but the hypotensive effect of Rauwolfia is at least additive to other hypotensive drugs. The resulting bradycardia tends to overcome the acceleration of the heart induced by hydralazine; its bowel-stimulating action may moderate the constipation from ganglionic block; its tranquillizing effects seem to make Veratrum effective with less vomiting. Smaller doses of the other hypotensive drugs are required if the patient is receiving Rauwolfia.

R. serpentina, therefore, seems to be a worthwhile drug in early, mild cases, especially if nervousness or tachycardia is prominent and psychotherapy is ineffective. In more severe cases, with headache, dizziness, or evidences of hypertensive cardiovascular disease, it may be useful alone but more likely in combination with other drugs. As Wilkins has stated, it should be the first (hypotensive) drug tried and the last omitted. No deaths have been reported from its use and even the severe side effects, such as depression, yield to withdrawal of the drug.

B. Veratrum Alkaloids. The Veratrum alkaloid esters are another group of hypotensive agents obtained from plants. Both hypotensive and side effects are similar whether one uses crude root, standardized alkaloidal extract, or purified derivatives such as protoveratrine A and B. In view of the narrow range between therapeutic and toxic doses (approximately 30 per cent) pure substances administered by weight are more desirable than biologically standardized material.

Study of the pharmacologic action of these drugs has revealed the existence of a reflex causing a fall in blood pressure and heart
rate from afferent stimulation of chemical receptors in the heart and great vessels (the Bezold-Jarisch reflex). 

The Veratrum esters elicit a veratrinic response (repetitive electric discharges of a single stimulus) in the chemoreceptors of the carotid sinus and coronary vessels. Increased afferent electric activity is transmitted via the carotid sinus and the vagus nerves to the central nervous system, which in turn causes a diminution in efferent electric activity over the splanchnic and presumably other sympathetic nerves. Hence, vasodilation and fall in blood pressure occur. Accompanying and increasing the hypotension is a bradycardia due to increased reflex vagal activity. A stimulating effect on the nodose ganglion in cats seems to be the source of the vomiting reflex. Toxic doses of the drug in man cause epigastric and substernal oppression, nausea, vomiting, sweating, marked hypotension, bradycardia, and even heart block or Extrasystoles. The disturbances in rate or rhythm are vagal phenomena and are readily overcome by atropine (0.5–1.0 mg. subcutaneously or intravenously). Ephedrine sulfate (25–35 mg. subcutaneously) or other vasoconstrictor drugs counteract an excessive blood pressure fall. At the height of the hypotensive reaction there may be transient electrocardiographic changes such as T-wave inversion in V2 and V4. These changes are reversed by atropine, but not by oxygen, indicating that they are due to vagal stimulation rather than to anoxia. There is no paralysis of autonomic activity and consequently interference with postural reflexes does not occur. However, if a toxic dose causing marked hypotension has been given, standing may cause a further fall in blood pressure. Cardiac irregularities are more likely in patients receiving digitalis or quinidine. Oliguria may occur during the hypotension from Veratrum, resembling that seen after any sudden fall in blood pressure, but it is transitory and not accompanied by fluid retention. Renal function is not adversely affected unless uremia is present. However, in some patients with nitrogen retention cautious lowering of the blood pressure may be achieved without much aggravation of the renal status. Once frank uremia is reached, any hypotensive measure will aggravate the renal insufficiency, but control of encephalopathy, headache, diminishing vision, and heart failure may be obtained.

Although there is a narrow range between the hypertensive and toxic or emetic dose, these alkaloids, particularly protoveratrine, can be given intravenously with only rare toxic effects. Vomiting is more likely to occur with subcutaneous or intramuscular administration and is even more common with oral drug therapy. Protoveratrine can be given intravenously with predictable results if dosage is based on the patient’s weight. The initial dose should be 1.5–1.9 μg. per Kg. followed by 20 μg. every 10 minutes until the blood pressure is satisfactorily lowered. Subcutaneous or intramuscular dosage is 4 to 6 μg. per Kg. given at 6 to 8 hour intervals. Parenteral administration may be compared to digitalization with a rapidly acting digitalis glycoside. Prolonged parenteral and oral administration presents the problem of increased incidence of vomiting, which limits the usefulness of this drug in treating chronic hypertensive disease to not more than one fourth of the patients. In this latter group the drug may be given for long periods without loss of responsiveness and only occasional episodes of nausea and vomiting. Because of the side effects, oral drug administration requires close supervision of dosage, usually with 3 or 4 daily doses i.e., a half hour after breakfast, at about 2 p.m., a half hour after supper and at bedtime. The dose must be worked out by trial, and an average initial program would be 0.5 mg., 0.25 mg., 0.5 mg., 0.25 mg. in 4 daily doses as above. Increments should be 0.125 mg. only. Hoobler and co-workers have recommended 1 large dose (0.5 to 1.5 mg.) after breakfast followed by 2 small doses (about 0.25 mg. each) at 2 to 3 hour intervals; a similar program starting after supper has been helpful in controlling nocturnal dyspnea.

The Veratrum alkaloids are probably the drugs of choice when prompt predictable fall in blood pressure without elevation of cardiac output or disturbance in homeostatic reflexes is desired. They are virtually specific in cases of pulmonary edema associated with acute
glomerulonephritis, hypertensive encephalopathy, the hypertension and convulsions of toxemia, and cortisone-induced hypertension. They may be a useful adjunct in the treatment of hypertensive congestive failure and are very useful in malignant hypertension with early or threatening loss of vision. In these instances the parenteral route should be employed. Of 9 patients with malignant hypertension treated with parenteral proto-veratrine, 5 had remissions and were alive 1 to 3 years later.20

Patients with congestive failure or coronary disease complicating hypertension who show a satisfactory hypotensive response to Veratrum alone or combined with reserpine will have alleviation of failure and decrease in angina. Despite the acute nature of the toxic effects and occasional marked hypotension, no deaths are known to have occurred from its use. It is probably the best drug for parenteral administration for short-term therapy of acute hypertensive states. Its mechanism of action would make it the ideal drug were it not for its tendency to cause vomiting.

C. Hydralazine. Hydralazine (1-hydrazinophthalazine, Apresoline) is a synthetic agent whose hypotensive properties were described only a few years ago.21 It is effective when given by mouth and appears to act on the central nervous system as well as against a number of circulating vasopressor substances. In animals, hydralazine exhibits sympatholytic activity, but in the doses used in man these effects are minimal. A marked increase in renal blood flow accompanies the moderate fall in systolic and diastolic pressure, yet it is not more effective in renal hypertension than in other varieties. It does not increase glomerular filtration rate and does not elevate to normal the depressed renal blood flow of essential hypertension.

A direct stimulating effect on the heart results in tachycardia and increased cardiac output, which explains the aggravation of angina pectoris and congestive heart failure often seen, even at lowered blood pressures. Although hydralazine may cause electrocardiographic changes of anoxia in patients with coronary disease, it is said to improve the contours of the ballistocardiogram, presumably because of peripheral vasodilatation. Rauwolfia or Veratrum should be used to slow the heart rate before hydralazine is given to patients with coronary disease or congestive failure. Some of the adverse cardiac effects of hydralazine may also be avoided if ganglionic-blocking drugs are used first.

Initial toxic symptoms include nausea, vomiting, some degree of postural hypotension, and headache. The last mentioned is common and often very severe but may be alleviated by antihistamine or analgesic agents. These symptoms usually subside in a few weeks and can be minimized by starting treatment with small doses. Continued administration has resulted in familiar types of drug reactions (fever, edema, rashes) and also a new type of drug reaction,22 a collagen-like disease that has appeared in 8 to 10 per cent of patients receiving large doses for a year. This syndrome may include arthritis, rash, fever, anemia, hematuria, enlarged lymph nodes and spleen, albuminuria, positive cephalin flocculation, and even "L.E." cells. It has appeared mainly in patients who have received large doses that effectively lowered their blood pressure. Thus far, apparently, even when "L.E." cells are present, the syndrome has disappeared when the drug was omitted and, in some cases, corticotrophin given.

Initial dose should be 25 mg. or less four times daily. Increments of 25 mg. per dose are added every 3 to 4 days unless severe headache appears. Maximum daily doses have ranged from 500 to 800 mg. a day. In view of the high incidence of drug toxicity it is doubtful whether more than 400 mg. a day should be given. If hydralazine is used alone, prolonged administration is not only accompanied by a rising incidence of drug toxicity, but a diminution in the number of good responses. Initially satisfactory hypotension is obtained in about one third of the cases, but after 1 to 2 years of treatment good results have diminished to one tenth. Milder forms of hypertensive disease may respond to small doses of hydralazine, especially in conjunction with Rauwolfia or Veratrum without a high incidence of toxic reactions. In general, large doses of hydralazine


should be reserved for patients with severe forms of hypertensive disease in whom other treatment is inadequate. In conjunction with hexamethonium, however, it has been a very effective agent in severe forms of hypertensive disease.6

D. Ganglionic-Blocking Drugs. Demonstration of the striking ganglionic-blocking action of tetraethyl ammonium ion (TEA) led to a search for related drugs suitable for use in hypertension. Extensive pharmacologic studies33 have given a good picture of the action of these drugs. Hexamethonium, its new prototype pentolinium [pentamethylene-1:5-bis-N-(N-methylpyrrolidinium)], and other related methonium compounds exert their action by interfering with cholinergic transmission at the ganglionic synapse and not at preganglionic or postganglionic structures. There is no paralysis of the effector end organs and they remain capable of reacting to a suitable stimulus. For example, the arterioles will constrict with noradrenaline; the salivary gland will secrete and the bowel contract with cholinergic drugs.

Interference with sympathetic nervous activity causes orthostatic hypotension and compensatory tachycardia in almost all patients. Blood pools in the legs and splanchnic area unopposed by reflex sympathetic vasoconstriction. This may be so severe as to cause faintness or even collapse. The patient should sit or, better, lie flat when such symptoms appear. Some degree of postural hypotension is considered essential to successful management and therefore cannot be considered a side effect. Smaller doses are required for patients who are up and about than those in bed. Alcohol, a large meal, vigorous exercise, hot weather, low-salt intake, mercurial diuresis, all tend to potentiate orthostatic hypotension. Other evidences of interference with sympathetic activity are seen in the increased susceptibility to certain stresses such as anesthesia and hypoglycemia. Less anesthetic agent is necessary in patients whose sympathetic nervous system has been blocked by methonium compounds. Similarly, the usual adrenalin-like reaction to hypoglycemia does not occur, the patient merely passing quietly into hypoglycemic coma. Interference with sweating may result in elevations of body temperature during warm weather; yet failure of reflex skin vasoconstriction may cause shivering in cool weather. Interference with potency, more severe in the older age group, is troublesome, but is relieved temporarily by omitting a dose of the drug.

Blockade of parasympathetic activity causes additional undesirable effects. Blurred vision and intolerance of bright light often require tinted eyeglasses with increased correction. Dryness of the mouth from decreased salivation is annoying; lessened intestinal motility progressing to severe constipation and even ileus, and urinary retention in the male patient with prostatic hypertrophy may be serious. Toxic reactions with oral medication are more severe and more difficult to treat because the oral dose is about 20 times the parenteral dose. Constipation must be avoided, especially with oral administration, because it may result in massive absorption of the drug from the gut, with resulting severe toxicity such as profound hypotension and a complete paralytic ileus.* Irritant or saline cathartics should be used to insure daily bowel movement. Failure to have a daily bowel evacuation calls for omitting the drug. Deaths have occurred from paralytic ileus and from cerebral or coronary thrombosis secondary to severe hypotension.

In their mild form all these symptoms are responsive to oral cholinergic drugs, such as pilocarpine (5 mg.), prostigmine (15 to 30 mg.), and urethane of β-methyl choline (Urecholine) (5 to 20 mg.).

As with many other new pharmacologic agents, hexamethonium has apparently introduced a new disease. A severe fatal pulmonary fibrosis31 has been reported in a small number of patients who received large doses of the drug. These patients show severe tachypnea and dyspnea, which is improved in the supine position. The syndrome is more common in the malignant phase of hypertension and in the Negro.

Pentolinium has the same actions and ill effects as hexamethonium. It is more potent on a milligram basis but has not demonstrated

* This reaction can be readily differentiated from mesenteric thrombosis because the pupils do not react to light and the skin is dry.
decisively greater freedom from side effects or margin of safety. Its duration of action is longer than hexamethonium, however, and this represents a distinct advantage in oral medication.25

Pentolinium is administered in doses of 20 mg. (of the bitartrate salt) after breakfast, in midafternoon, and at bedtime. The dose is increased by 20 mg. slowly every few days until faintness in the upright position occurs, at which time slight reduction in dose is made. Tolerance occurs readily, both by mouth and parenterally, and during initial phases of treatment the dose must be increased. Eventually a stable dose is reached, but frequent adjustment, even diminution in dosage, is not uncommon. The desired effect is a systolic pressure not lower than 120 in the erect position.25 Some investigators recommend home blood pressure readings,6, 26 to obviate the notoriously unreliable "office" reading and to adjust medication on the basis of these home readings. Smirk25 believes that subjective faintness or lightheadedness in the erect position is a satisfactory guide to dosage. With pentolinium the three daily doses need not be equal; study of the blood pressure response may indicate the desirability of making the bedtime dose larger and the dose after breakfast smaller than the midafternoon dose. Education of the patient so that he understands the effects and side effects of the drug is essential to good control. Satisfactory levels of blood pressure may be reached in two thirds or more of patients; one third may have normotensive readings in the erect position. Recently, a new synthetic ganglion-blocking drug, Meborylamine, has been introduced for study. It has a longer duration of action than pentolinium and is completely absorbed from the intestinal tract.

Contraindications to therapy with ganglionic-blocking agents include (1) uremia, which is always aggravated, (2) prostatic symptoms, (3) generalized and, especially, advanced cerebral arteriosclerosis, (4) recent (6 to 12 weeks) coronary or cerebral thrombosis, (5) pyloric stenosis and (6) lack of cooperation or poor intelligence of the patient.

Patients who exhibit the malignant phase of hypertension, congestive failure, or other evidences of severe hypertensive disease should be treated with ganglionic-blocking drugs, preferably in conjunction with Rauwolfia or hydralazine,6 if simpler measures have been tried and are ineffective.

E. Choice of Drug Combinations. Combinations of hypotensive drugs appear to be more effective and better tolerated than any single one of the drugs available today.27 The undesirable effects of some of these are mitigated, probably because smaller doses of each are necessary, and because some tend to overcome adverse effects of others. The more powerful drugs are more dangerous and they should be employed only when simpler measures have had adequate trial.

For the patient with mild, asymptomatic, early hypertension, but no evidence of cerebral, heart, or renal disease, psychotherapy and reorientation to the stresses of life are adequate therapy. For the patient with hypertension proved benign by its long duration, especially elderly persons with only moderate degrees of left ventricular enlargement or 1+ albuminuria, again only firm reassurance is necessary. If symptoms not responsive to psychotherapy or phenobarbital are present, Rauwolfia can be employed.

Patients who show sustained high diastolic pressure, especially men, or have evidence of progressive but not malignant hypertensive disease should receive hypotensive therapy. Rauwolfia should be tried first. Next, sodium restriction (200 to 500 mg.) should be added. Failure to respond to this regimen in 2 or 3 months is indication for use of Veratrum (or protoveratrine) and later, if necessary, ganglionic-blocking drugs.

Patients with hypertensive cerebrovascular disease may be given Rauwolfia, low-sodium diet, Veratrum or small doses of hydralazine, in that order. The use of these drugs for acute cerebral accidents, such as hemorrhage, is still experimental.

Hypertension and coronary artery disease may be treated with Rauwolfia, salt restriction and Veratrum. Ganglionic-blocking drugs cautiously administered to lower pressure gradually and not too far, with the addition of small amounts of hydralazine, may give remarkable relief.
The development of congestive failure, or the malignant phase of hypertension, unresponsive to salt restriction or Veratrum calls for the addition of ganglionic-blocking drugs, such as hexamethonium or pentolinium and hydralazine.

For acute hypertensive crises Veratrum (or protoveratrine) is the drug of choice. Intravenous sodium nitroprusside has been recommended recently.\textsuperscript{28} Ganglionic-blocking drugs are also often effective, but not so easily controlled and less desirable in cases such as eclampsia, where anesthesia may be utilized or precipitous blood pressure falls are to be avoided.

One half or more of patients with malignant hypertension can now expect reversal of the accelerated phase of the disease, if uremia is absent.\textsuperscript{5, 6} from combinations of drugs or surgery. All forms of therapy fail in hypertension, once uremia is present; but mild degrees of nitrogen retention occasionally respond dramatically to drugs or diet. Once these agents have induced a satisfactory hypotensive effect, it is important that therapy not be stopped abruptly, especially in patients with malignant hypertension, lest uremia, cerebral hemorrhage, or heart failure be precipitated.

4. Surgery

Unfortunately, treatment with drugs or diet is not always effective in hypertensive disease. For some severely ill patients, it may be desirable to recommend surgery. No patient should have a sympathectomy or adrenalectomy without a prior trial of drugs, including ganglionic-blocking agents.

After more than two decades of experience with resection of portions of the sympathetic nervous system for hypertension, popularity for this procedure seems to be declining. This is primarily because there is still no agreement on the best operation nor are there valid criteria to indicate which patients are likely to benefit by the operation.\textsuperscript{29, 30} In a careful study, Hoobler and co-workers\textsuperscript{31} were unable to indicate any clinical differences between patients who did well after sympathectomy and those who did not. In addition, prolonged morbidity may follow the operation. Although surgeons claim that one half of their patients are helped by this procedure, most medical men feel that the maximum figure is one third and many believe it is no more than one tenth. Sympathectomy was clearly the first procedure, however, to alter the poor prognosis in malignant hypertension. There is not yet agreement that life expectancy in milder degrees of hypertensive disease is increased. Lack of knowledge of the life history of untreated cases and the difficulties in prognosticating for the individual patient, make it as difficult to evaluate results of sympathectomy as of other treatment programs.

The variety of surgical procedures recommended has extended to virtually total sympathectomy. This last procedure represents formidable and multiple surgery, and most surgeons do not believe it offers more than the less extensive operations. The most widely used surgical procedures are those of Peet\textsuperscript{32} and of Smithwick.\textsuperscript{33} The former is often done in one stage; it does not entail prolonged morbidity from postural hypotension and does not interfere with ejaculation. The sympathetic chain, from the sixth to the twelfth thoracic, including the splanchnic nerves, is resected on both sides. Portions of two ribs must be removed and the operative mortality is three per cent. The Smithwick procedure includes the lumbar ganglia, thus resulting in postural hypotension and interference with potency. This procedure has the advantage of exposing the adrenal glands, to detect a rare instance of pheochromocytoma, as well as the kidneys. Both procedures may cause severe persistent postoperative neuritis. There is disagreement concerning the necessity of postural hypotension for a good therapeutic response with improvement in survival rates. Kahn\textsuperscript{34} found no significant difference between the survival rates in Peet’s and Smithwick’s series; yet one of the alleged requirements for good result with “medical sympathectomy” is some degree of postural hypotension. Lowered blood pressure should persist for a year before the operation can be considered successful.\textsuperscript{31}

While the exact role of sympathetic surgery remains unsettled, having been displaced to a large extent by ganglionic-blocking drugs, there
are a few situations in which operation should be recommended. Any patient with malignant hypertension not responsive to medical treatment within a reasonable period (e.g., 2 to 3 months) should have sympathectomy if nitrogen retention is absent. Surgery is invariably unsuccessful when nitrogen retention is present. Sympathectomy should be advised for patients with evidence of rapidly progressive but not necessarily malignant phase of hypertension who cannot be followed very closely, live far from good medical attention, and lack the intelligence and cooperation necessary in using the more potent hypotensive drugs or have not responded to medical treatment. Apparently sympathectomy increases the effectiveness of drugs and diet.

Adrenalectomy, with or without accompanying splanchnic resection, is at present an experimental procedure. The good results reported can often be equaled by sympathectomy alone or with sodium restriction. In such patients, strict low-sodium intake, with additional measures if necessary to cause negative sodium balance (mercury, resins), and ganglionic-blocking drugs should be equally effective. Patients whose adrenal glands are removed face the life-long likelihood of acute serious illness with infection, stress, or omission of cortisone. Moreover, some patients may show simultaneously high blood pressure and the serum chemical derangements of adrenal insufficiency, not to mention the hazards of cortisone psychosis and metabolic accidents.

From the empirical and varied nature of the treatment outlined above management in hypertensive disease is obviously far from ideal. The physician's problem is complicated by (1) lack of uniform classification of hypertension in terms of etiology, severity and complicating vascular disease; (2) inadequate data on life history and inability to prognosticate for the individual case; (3) lack of agreement concerning indications for treatment, choice of treatment and the results of treatment and (4) the dangers and discomfort of this therapy. Nonetheless, with proper exercise of his science and art, always bearing in mind non nocere, the physician can do more for hypertensive patients than ever before. Measures successful in lowering blood pressure will alleviate, and possibly prevent, many of the serious sequelae of this disorder.

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