Cardiovascular Conferences of Howard University and Freedmen's Hospital, II*

Hypertension

Current Status of Therapy — Hope for the Future

EDWARD FRIES, M.D.
Clinical Adjunct Professor of Medicine, Georgetown University

HYPERTENSION involves a syndrome which probably has diverse origins. Some of the etiological factors we know, but with the great majority of patients with hypertension we do not know the causative factors. This makes treatment difficult. The few types of hypertension in which the cause is known may be mentioned. It is important to recognize that some are curable.

CURABLE HYPERTENSION

The form of hypertension seen more in children than in adults is coarctation of the aorta. Anyone who is examining children should bear in mind the possibility of this diagnosis since, the operative risk is much less in the young and removal of the coarctation will result in complete cure. The prognosis in coarctation without operation is very poor, most patients dying around the age of 45. It is important to make a habit of palpating the femoral artery. If femoral pulsations are small (in comparison with the radial), further study should be made to rule out the possibility of coarctation.

The second and most interesting form of curable hypertension, is pheochromocytoma. This benign tumor of the adrenal medulla occurs in less than 5 cases of hypertension out of 1000. Nevertheless, when the diagnosis is made early a complete cure can result after removal of the pheochromocytoma. Complete cure does not always result, however, especially if the hypertension has been established for many years. In any individual below the age of 45, who has established hypertension whether it be labile or permanent, some sort of screening test should be done to rule out the possibility of pheochromocytoma. The best screening test in current use is the Regitine test. The package which accompanies the ampule of Regitine gives full directions as to how to perform and interpret the test. If the test dose is given intravenously there is a chance that the patient will become apprehensive so that the control blood pressure will be falsely high, and even though no pheochromocytoma is present a false-positive test may result. We prefer to use the intramuscular test, having the patient's blood pressure taken by the nurse before he has any knowledge that the test is to be done. Following the intramuscular injection the patient's blood pressure is checked at least every ten minutes for an hour.

The third type of curable hypertension is that connected with unilateral renal disease. In suspicious cases all of the various diagnostic tests should be carried out. In the past two years, I have seen a number of such cases and the results of removing the kidney has been very satisfactory in the majority. One of these patients was a physician who had a seminoma of the testicle removed and heavy doses of x-ray over the left kidney. Following this he developed fibrosis in that area producing a contracted left kidney and then developed hypertension. The kidney was removed and the hypertension disappeared. His pressure has remained so for the past two years. I have seen a young girl of six years who had unexplained, extremely severe hypertension. The tests for pheochromocytoma were negative and the only abnormality found was that one kidney was smaller than the other. At operation there was nothing specifically wrong with this kidney except that it was congenitally small. It was removed and this patient has had no further hypertension over a period of the last year and half. The intravenous pyelogram is the most satisfactory screening test for determining whether or not the kidney is normal or whether unilateral disease exists. It is important that the kidney be removed early because the longer the hypertension is established, the less likely it is to disappear after the diseased kidney is removed.

* Conference of February 26, 1956.

Another very common cause of severe hypertension is that associated with chronic pyelonephritis. This hypertension if very severe, often becomes malignant, and is most difficult to treat by any of our present methods. Another difficulty associated with chronic pyelonephritis is that once the hypertension has become established, the infection is already so well entrenched in the kidney, that it usually cannot be eradicated with antibiotics or other types of therapy. It is almost always bilateral. If unilateral, then consideration should be given to removal.

In our experience, the treatment of the underlying chronic bilateral pyelonephritis after the patient has developed severe hypertension has been very disappointing. It is a major problem in preventive medicine. It behooves the physician to treat his cases of acute pyelonephritis adequately and thoroughly. Very frequently we get the story that the patient has been treated for his pyelonephritis but only for a short period. It is a common observation that when one treats pyelonephritis with antibiotics the urine will clear rapidly; but, if the patient is seen a month later, you will find in some cases that the infection has not been completely eradicated and flourishes again. Therefore, following the patient—two weeks, a month and several months later—to be certain that the infection has been completely arrested, is quite important. It is also vital that treatment be adequate and continued for at least a week or two after all signs of infection disappear from the urine.

There is one other form of curable hypertension associated with renal disease which again is very rare and of which I personally have seen only one case. It is an extremely difficult diagnosis to make. This is infarction of a portion of one kidney. The case was in a woman who had mitral stenosis. Following mitral valvulotomy a thrombus in the auricle broke loose. After operation she developed acute pain in the left flank and hematuria. Thus there was good evidence that the thrombus had lodged in the left kidney. This patient developed an acute hypertension which persisted. The diagnosis was made by aortography. Dye going into the renal arteries on both sides showed an area of the left kidney that was not perfused with dyed blood. This patient's kidney was removed.

There is also a hypertension occasionally associated with tumors of the adrenal cortex or hypophysis. This usually is associated with central obesity, striae on the abdomen, osteoporosis and the other symptoms and signs associated with Cushing's syndrome. It usually is obvious on looking at these patients that they have hypertension due either to adrenal cortical hyperplasia, adrenal cortical carcinoma or a tumor of the pituitary which produces secondary hyperplasia of the adrenal cortex. Recently the new syndrome, aldosteronism, has been described. A small cortical adenoma is present which produces an excess of aldosterone. This produces a characteristic syndrome of muscular weakness, changes in the electrolytes and hypertension. It is curable on removal of the adenoma.

ESSENTIAL HYPERTENSION

There are other known causes of hypertension for which we have no adequate treatment. These include chronic Bright's disease, chronic glomerulonephritis or any type of renal disease where there is damage to the renal parenchyma. Incidentally, hypertension due to renal disease is very severe and difficult to treat. In the remaining 90 to 95 per cent we do not know the cause. We call this large group essential hypertension.

The treatment for essential hypertension is limited because we do not know the cause. The most effective therapy is accompanied by discomforting side effects. It is often expensive and the treatment must be applied for the rest of the patient's life since we are dealing with a chronic condition. Adequate therapy requires a good deal of knowledge and care on the part of both the physician and the patient to apply properly. Before embarking on the course of therapy one has to make a decision between how important is it to treat this patient and how difficult therapy is going to be. These two factors are balanced one against the other.

In order to decide how important it is to treat the particular patient, that is, lower his blood pressure, one must use many other criteria than simply the level of the blood pressure as recorded in the office. The level of the blood pressure as recorded in the office is probably one of the least important of the various criteria on which to base a prognosis. Included in a group of syndromes that we call essential hypertension are conditions which produce no symptoms, no organic complications and do not prevent the patient's living out a normal span.

This is the mildest form of essential hypertension. Then one sees all gradations of severity to the patients who develop hypertension and within a month are dead from uremia and heart failure. Therefore, we must be selective. We must select those patients whom we believe will not fare well, who will develop serious complications, or who will die within five years if not placed under some form of treatment. On the other hand, we should omit those types who will do well regardless of whether we treat them or not. They will not develop serious complications, their lives will not be greatly shortened by the hypertension and their treatment will be entirely different than that for the patient who has serious and accelerated disease.

An important factor in our decision is the patient's age. In general and quite paradoxically, the younger the individual, for a given level of blood pressure, the more serious the prognosis. It is not uncommon to see in very aged people, above the age of 70, elevated blood pressure of extreme degree, e.g., 250/130, which is supported by the patient with no symptoms and without any complications. These patients may do well for a number of years. On the other hand a blood pressure of 200/120, in an individual in his 20's always has a serious prognosis. This patient certainly will develop complications unless he is treated.

Another important criterion is the sex of the patient. In general, females tolerate hypertension better than males and live longer with it than do males. For any given level of blood pressure they seem to fare better than males in regard to the complications of the disease.

Perhaps the most important of all the prognostic criteria is the examination of the eye grounds. It is there that we can see blood vessels, and can estimate how much organic damage is occurring in the arterioles as a result of hypertension. If I had to make a choice between the blood pressure apparatus and ophthalmoscope for evaluating hypertension I would throw away the blood pressure apparatus and keep the ophthalmoscope.

The various classifications are already familiar to you. Grade I is moderate narrowing of the arteries. Grade II is narrowing and thickening of the walls to the point where there is compression of the veins at the point where the artery crosses (so-called AV nicking). Grade III includes the additional complication of hemorrhages or exudates in the optic fundi, and Grade IV the further complication of papilledema, that is, edema of the nerve head at the optic disc. It is only when the latter is present that we use the term "malignant" hypertension. If edema of the nerve head is not present, we do not use the term, regardless of the height of the blood pressure, the number of hemorrhages or exudates in the fundi or the severity of the renal damage.

More important than the level of the blood pressure as recorded in your office, or in the clinic is its lability. It is common observation that a patient, particularly a female, may have extremely high levels of blood pressure as recorded in the office or clinic, who may live for many years without complications. If, however, such individuals are placed in the hospital and the blood pressures are recorded four or five times daily by nurses, we find that the blood pressure falls remarkably, in fact it may fall to normal. There are a group of hypertensive patients who have elevation of blood pressure only under stress. This elevation can be quite severe. Under the stress of the visit to the doctor's office they will exhibit this transient elevation, whereas at other times they do not. We have recorded blood pressure in the home in a number of cases who have normal pressures in the hospital and high pressures in the office or clinics and find that the home pressures agree with the hospital pressures. In other words, these patients do not have severe hypertension at all, they only have very transient elevations. These patients have a far better prognosis than the patient who has more moderate levels of blood pressure in the doctor's office but who has them also at work and at home both day and night.

Another method for evaluation lability of the blood pressure is the so-called sodium amytal test. The patient is hospitalized and given three grains of sodium amytal every hour for three hours following which the blood pressure is recorded every hour through the night. In individuals with labile blood pressure marked reductions usually occur. I believe that such patients show similar falls every night when they fall asleep, whether they are given amytal or not. There is nothing specifically hypotensive about sodium amytal. It merely is a way of putting a patient to sleep so that his blood pressure can be taken during sleep. These patients, as a rule, live longer, have less

complications, and do better than the patients who maintain a persistent level of hypertension.

What we are getting around to is this: the office level of the blood pressure is not so important as the average level that is maintained both day and night. It is the continuous application of high pressures in the arterial tree which seem to produce organic damage. In the patients with occasional bouts of high pressure damage occurs more slowly or not at all.

Another important criteria for judging prognosis is the effect of the hypertension on the heart. The heart is like any other pump. If the resistance is increased, then it has to work harder to pump the same amount of blood. If it has to work harder it must hypertrophy and dilate. This process goes on until it can no longer compensate by further hypertrophy and dilatation and therefore the left ventricle fails.

Hence, in judging the effects of the hypertension on that particular individual's heart one should estimate the degree of hypertrophy and dilatation as an index of how much strain has been on the heart thus far. The history is important. One should ask the patient whether he gets out of breath with moderate exercise; how many stairs he can climb before he gets out of breath; and whether he awakens at night with shortness of breath. The greater degrees of cardiac decompensation will be manifested by orthopnea and particular in hypertension by paroxysmal nocturnal dyspnea. These always are signs of advanced cardiac dilatation, hypertrophy and failure. The milder degrees may be detected by the electrocardiogram and x-ray of the heart.

Renal disease as a cause of hypertension has been mentioned. It also should be borne in mind that essential hypertension, when long established, can produce renal disease. The process of sclerosis of the arterioles of the kidneys progresses in severe cases to the point where renal deterioration begins to set in. Damage to the renal parenchyma results. Then a second aggravating factor enters. In addition to essential hypertension we now have renal damage accelerating essential hypertension. Once this complication occurs treatment of essential hypertension becomes much more difficult and the hypertension much more resistant. Thus, nephrosclerosis is a serious development as far as prognosis is concerned.

To judge the amount of renal involvement, one should first determine what one can do from the history by asking these patients whether they have any nocturia. Many hypertensives have nocturia which may not be on the basis of renal disease. They may have nocturia because they do not sleep well and wake up frequently to void small amounts. They may have nocturia because they have cardiac failure. During the day when they exercise their cardiac outputs are not adequate for the demands, renal blood flow decreases and they develop oliguria. At night when at rest their hearts have a better chance to compensate, and so renal blood flow and filtration rate increase. More urine is formed and nocturia results. Thus, nocturia must be analyzed in terms of whether it represents true renal damage or not. The surest way to determine the presence of renal damage is with the aid of the laboratory. Renal function tests are extremely useful for judging the prognosis. Urinalysis is helpful especially in determining the degree of albuminuria, fixation of specific gravity and the character of the sediment. The 15 minute and one hour excretion of PSP dye are also valuable provided the patient is well hydrated before the dye is given, so that he is able to excrete an ample supply of urine. In any young hypertensive the intravenous pyelogram is necessary to rule out those patients with unilateral renal disease.

Another prognostic guide is the degree of acceleration of the hypertension. If the hypertension has remained stable for many years and there have been no signs of organic damage the outlook remains good. But if suddenly, and this can happen at any time, the blood pressure levels become higher, the fundi show an advance from Grade I to Grade II or Grade I to Grade III then the prognosis becomes much more serious. The choice of treatment must then be changed.

If we judge the prognosis to be good, and are dealing with a mild benign hypertension in a middle aged female, our treatment should be limited primarily to symptomatic therapy. We certainly should reassure the patient that this is not the hypertension that her uncle died of, but a much milder form and that her outlook is entirely different and much better. We can use Rauwolfia preparations in such an individual and occasionally they are most helpful in the milder forms of hypertension and produce a reduction in blood pressure

with symptomatic improvement. These patients are frequently high strung, irritable individuals. The use of Rauwolfia may produce a little of the "manana" attitude in them which is most helpful. On the other hand the response to Rauwolfia may be quite the reverse; the patient may feel depressed, lethargic and lose the joy of living. In these individuals it is better to discontinue the Rauwolfia, as a matter of fact we have seen serious mental depression (about 6 to 7 per cent) develop in patients who have had Rauwolfia for a long period of time. I have heard of four suicides with the use of the drug, one in our own group of cases, so that this drug is not quite as benign as we were originally led to believe. The possibility of a depression always must be borne in mind when giving the drug. Nevertheless, despite this minority of patients who develop depression, there are a great number of patients who derive benefits from it, and the drug therefore, should be used but with care and knowledge.

On the other hand if we are dealing with a young patient who has Grade III fundi, let us say, early cardiac enlargement and albuminuria, we should treat this patient as intensively as we can, because the chances are very good that he will develop serious complications within a short period.

DIET, SYMPATHECTOMY AND DRUGS

The types of treatments used in the past in these serious cases have been primarily diet and or sympathectomy. Diet therapy is based on severe restriction of salt. In order to be effective, salt must be restricted to less than 200 mg. of sodium per day. If more is given lowering of blood pressure will not occur. The rice diet has a sodium content of about 100 mg. of sodium per day and for that reason has been effective in reducing blood pressure in abut 30 to 40 per cent of patients with severe hypertension. The difficulty with all of these diets is that the patient will not stay on such a strict regime. You may keep them on it for a couple of weeks especially in the hospital, but when they leave the hospital and return to their normal environment they revert, in my experience, to a moderate salt restricted diet which is little better than no restriction of salt. We have given up those diets as a method of treating hypertensive patients except in the patients with heart failure.

Sympathectomy enjoyed a great vogue until recently and is still an effective procedure in about 30-40 per cent of hypertensive patients. The reason it has fallen out of vogue is that it is difficult or impossible to determine which patient will respond well to sympathectomy and which will not. In addition it produces a good deal of post-operative disability for a period of several months. There often is considerable pain associated with the immediate post-operative period. Yet, there is no guarantee that after the patient goes through all this he will derive benefit. Nevertheless, we still advise sympathectomy in the patients who will not cooperate in a drug regime and in whom we think that some form of hypertensive therapy is required.

As a result of the unpredictability of sympathectomy and the difficulty in keeping the patient on a low sodium diet, drug therapy has become more popular in recent years. Too much must not be expected from this form of therapy. It is still new. It is by no means as effective as giving penicillin for infection or insulin to a diabetic. In addition, the more effective the therapy the more difficult it is to administer without side effects. Nevertheless, it will produce the greatest degree of reduction of blood pressure in the greatest number of patients. Another advantage is that we do not commit the patient to a serious operation which may not be effective. If properly administered, the patient can tolerate drug therapy better than a low sodium diet over long periods of time. The disadvantages of drug treatment are that it means that a patient has to take medication for the rest of his life and also that these medications are expensive. If you added up the total amount of money spent on controlling that patient for the rest of his life, it would be much more expensive than a sympathectomy. The side effects and the care that is needed to apply these drugs effectively also pose special problems.

RESULTS OF DRUG THERAPY

We have been treating hypertension with drugs at Georgetown and Mt. Alto Hospitals since 1949. Last fall we analyzed our cases of malignant hypertension that had been treated with drugs for three years or longer to see how many of these survived and how they compared with a group of untreated hypertensive patients. We excluded from our treated series those patients who entered the hospital

obviously in a terminal condition with advanced uremia and who were dead within two weeks or so whether they were treated with drugs or left alone. This is a selected series of treated cases in the sense that the terminal cases are not included. Here is the follow-up of the untreated series of malignant hypertensives, that is, patients with papilledema and very severe diastolic hypertension as described by Keith, Wagener and Barker. At the end of a year in the Keith series, only about 18 per cent of the 146 cases survived. At the end of a year in our series about 65 per cent of 64 cases survived. At the end of two years 10 per cent in the Barker series and 48 per cent in our series survived. It would appear that our treatment has been of some benefit in prolonging life in the most severe types of hypertension. Dr. Smirk in New Zealand has published similar data also pointing toward a definite prolongation of life in malignant hypertension.

It is interesting to see that as our treatment improves apparently our results improve. There were 20 malignant cases who were placed under treatment in 1949-1950. They did not fare as well as the group put under treatment in 1951-1952. In the period from around 1950-1951 we began to use the treatments that are used today—ganglionic blocking agents, Apresoline and Rauwolfia.

DRUGS FOR HYPERTENSION

The is no dearth of drugs that have been discovered for the treatment of hypertension. There has been a dearth of good drugs but there has been no paucity of agents. Drugs have been developed which act at different sites. This is of interest in determining or projecting our thoughts as to the type of agents we should like to develop in the treatment of hypertension. First, there are drugs that act on the blood vessel itself. An example is sodium nitrite. One would think that a drug which dilates blood vessels would be highly desirable for treating hypertension. As a matter of fact, it does not seem to be because it dilates not only arterioles but also capillaries and venules as well. The net effect is that blood is pooled away from the heart. The sympathetic nervous system then becomes very active, producing tachycardia, compensatory constriction and the patient develops side effects which are decidedly uncomfortable. They also develop postural hypotension from pooling blood and quickly develop tolerance to this form of drug therapy. I do not think that the vasodilators are useful because they leave undisturbed all the compensatory mechanisms of the body which come into play to restore the previous level of blood pressure.

Next, there are those drugs which block the adrenergic system. At the endings of the sympathectic nerves on the blood vessels a substance is secreted which produces vasoconstriction. This substance is believed to be nor-epinephrine. Nor-epinephrine and epinephrine also are secreted by the adrenal medulla so that all drugs which act to block the sympathectic nerve endings at the blood vessels also neutralize the effect of circulating epinephrine and nor-epinephrine from the adrenal medulla. Examples of such adrenergic blocking agents as Dibenamine, Priscoline and Regitine. These drugs have been unsuccessful in the treatment of hypertension. They also produce a marked postural hypotension and compensatory tachycardia and tolerance quickly develops when they are used. They are most useful for a screening test in ruling out pheochromocytoma.

The most effective agents that we have developed so far have been the drugs which block the transmission of impulses that cross the synapse in the autonomic ganglia. It is believed that acetylcholine is released by the afferent endings in the ganglia, which stimulates the cell bodies of the efferent sympathetic or parasympathetic nerves. The ganglionic blocking agents compete with acetylcholine and so inhibit at least a portion of this transmission across the synapse. Since in both the sympathetic and parasympathetic ganglia transmission is via the acetylcholine mechanism, the patient may have all the side effects of sympathetic and parasympathetic blocking. In addition, since acetylcholine is released by the parasympathetic system at all nerve endings, the parasympathetic side effects may be dominant. Thus, we frequently see in such patients loss of gastrointestinal tone with constipation due to the paralysis of parasympathetic nerves to the gut. We may have dilatation or fixation of the pupils with inability to constrict to light or to accomodate to near vision so that the patient may develop blurred vision on reading and experience difficulty when exposed to bright sunlight. Another effect of parasympathetic blockade may be dryness of the mouth due to blockage of the stimu-

lating nerves to the salivary glands of the mouth. Thus, these agents while very effective in controlling blood pressure, may produce many side effects. The first such agent developed many years ago was tetraethylammonium and the first practical blocker in the treatment of hypertension was hexamethonium. More effective blocking agents now are available such as pentolinium tartrate, Ecolid and mecamylamine.

There is another group of drugs which activates an unusual cardiovascular reflex. These stimulate afferent nerve endings in the myocardium of the left ventricle and also in the lung and carotid sinus. The impulses ascend to the vasomotor center and then out over the vagus to produce slowing of the heart and also over unknown pathways to induce dilatation of blood vessels and a fall in blood pressure. Such alkaloids are obtained from Veratrum viride, from mistletoe, and from certain other plants. They are not too effective in treatment because in dosages close to the dose which produces this reflex hypotension there is stimulation of the emetic center. Nausea and vomiting are frequent complications of the hypotension produced by these agents. Nevertheless, in certain short-term treatment problems they may be quite valuable. Their greatest advantage is their safety. As much as ten times the effective dose has been given intravenously without any serious complications resulting therefrom. Although these patients may become violently ill with nausea, vomiting and extreme hypotension, they always recover. There is not a single case in the literature (and this drug has been used since 1850) of a death from the use of Veratrum viride. Because of its safety, it is frequently used in the treatment of hypertensive toxemia of pregnancy where it need only be used for short periods of 24-48 hours and also in acute nephritis where the individual has a temporary elevation of blood pressure during the acute phase.

There are some drugs which seem to depress the vasomotor centers directly. Examples are the dehydrogenated alkaloids of ergot and toxic doses of pentaquine. The ergot alkaloids have not remained effective over a long period of therapy. Pentaquine has been too toxic. It may be in the future that better drugs will be developed that act at this level.

The reason that we are interested in development of such drugs is that the response seems to be well integrated. The higher the level at which the hypotensive agent acts, the more integrated is the response, i.e., the more it resembles a normal reduction of blood pressure. There are less compensatory mechanisms thrown in to attempt to restore the blood pressure. It is my belief that at the moment we should concentrate on the development of agents which will act upon the blood pressure regulating centers themselves. We know that there are centers above the vasomotor centers in the medulla that control or influence the vasomotor centers. There is some evidence that Rauwolfia acts at this level, but it is not potent enough. It also is interesting that hemodynamic effects of hydralazine are exactly similar to pyrogen or fever therapy which apparently acts also in the hypothalamus.

The problem has been that the most effective agents, namely the ganglionic blocking agents, have also produced the greatest number of side effects. The problem has been to work out a regime which the patient will be able to tolerate for many years. One of the first steps was to determine whether by combining the ganglionic blocking agents with other hypotensive agents we would reduce the incidence of the side effects. We had a series of 96 patients with severe hypertension who were treated with pentolinium alone, pentolinium with Rauwolfia, pentolinium (trade name—Ansolysen) and hydralazine (trade name Apresoline) and all three of these agents The greatest incidence of side effects—impaired visual accommodation, dryness of the mouth, uncontrolled constipation, constipation controlled with laxatives and neostigmine, postural hypotension, syncope and sexual impotence —were most frequent when pentolinium was used alone. In general, the greatest reduction in side effects occurred when the three drugs were used together.

Not only were the incidence of side effects reduced but a slightly greater reduction of blood pressure was produced with combined therapy. We noted that when we used all three drugs the greatest reduction in blood pressure was obtained with the lowest dosage of the ganglionic blocker. The average daily dosage requirement in the group of patients treated with pentolinium alone is about 900 mg. whereas, in the group treated with all three drugs combined, it was better than 420 mg. Probably that is the reason that the side effects

were less pronounced and less frequent because less of the blocking agent had to be used to lower the blood pressure.

We should review Rauwolfia and hydralazine if we are to use these drugs with the ganglionic blocking agents. As a rule Rauwolfia is most effective against emotional and mild degrees of hypertension. The great advantage is that the dosage adjustment is so simple that it is almost a standard. We usually begin with 0.25 mg., 2 to 4 times a day for a week or two and then reduce the dose to 0.25 mg. per day. The reason for reducing the dose is that a higher incidence of lethargy and depression seems to occur when the patients are maintained on large doses for long periods. The hypotensive effect is about as good as other methods once the initial 2 weeks of therapy is completed. A small maintenance dose usually is sufficient in the responsive cases.

The acute side effects are mild and include sleepiness, stuffiness of the nose, increase in appetite, some frequency of bowel movements and nightmares. The chronic side effects are depression and we have also seen a few cases of unexplained gastrointestinal hemorrhage.

The acute side effects of hydralazine also are relatively mild but there are some serious chronic side effects. The acute side effects are headache, tachycardia, palpitation and dyspnea on exertion. These can be avoided in large measure if one begins first with a ganglionic blocking agent or Rauwolfia and later adds hydralazine. Dosages are increased gradually beginning with 25 mg. three or four times per day or 10 mg. three or four times per day, and increasing to 50 mg. per day or stopping at 25 if there is some reduction in blood pressure. Elevating the dosages over intervals of a week or two instead of days, can obviate these side effects. The late toxic effect I think also can be avoided in large measure. These include arthritis and a syndrome which resembles lupus erythematosus. Fortunately, if the drug is discontinued, the syndrome will disappear. We have not seen the development of the lupus-like syndrome in our cases. I think the reason is that we have avoided the use of large doses over a long period of time. We have seldom given more than 200 mg. per day and only on very rare occasions have we gone as high as 300 mg. Lupus can occur on such dosage but its incidence seems to be reduced.

There are methods of making drug treatment tolerable to the patient. First we have already cited the combination of drugs to keep the dosages low. Secondly, patients who have difficulty with visual accomodation are sent to a 5 and 10 cent store for glasses with 1+ or 2+ diopter lens. They may require the glasses only for a period of a month or two, because the blurring will frequently diminish as treatment proceeds. If they take some fine print along with them down to the 5 and 10 cent store and try on the various glasses there, until the print clears up they can usually take care of this side effect for about 25 or 50 cents. They also may require dark glasses to wear when they go out in the bright sun-light.

Constipation is a problem with the ganglionic blocking drugs and is managed in the great majority of patients with the use of laxatives at night and neostigmine orally in the morning before breakfast. For laxation we use a combination of mineral oil and milk of magnesia or cascara sagrada. We also tell the patient to drink much water and eat prunes. If this is unsuccessful the patient is instructed to take one to two tablets of neostigmine in the morning on an empty stomach. A bowel movement will frequently result about an hour thereafter. The dose is variable from one individual to another and has to be determined by trial, beginning with one tablet and increasing.

We do not deprive our patients of salt unless they are edematous. If they are on a ganglionic blocking agent they tend to develop postural hypotension. A certain degree of reduction of blood pressure when the individual stands up seems to be desirable because it tends to keep the blood pressure reduced when the patient is up and about during the day. However, when carried to extremes it may result in fainting. The effect of restriction of salt is to increase greatly the degree of postural hypotension. Patients who are on markedly restricted diets, such as the rice diet, and ganglionic blocking agents, often will develop incapacitating postural hypotension in dosages below the level required to reduce the supine blood pressure. We may use moderate restriction of salt, particularly in the cardiac patients. Of course if they have edema we use the same salt restricted diet that one would prescribe for that patient if he were not taking a ganglionic blocking agent. The non-cardiac, non-edematous individual has enough dif-

ficulty with the drug as it is and we might as well let them have the pleasure of eating tasty foods.

There are few patients who develop severe dryness of the mouth and in those individuals, pilocarpine nitrate in 5 mg. tablets taken one half hour or an hour before meals will often be effective in doing away with this side effect.

Two new ganglionic blocking drugs, hexamethonium and pentolinium (Ansolysen), are on the market. In each the nitrogen group contains a valence of five. All compounds which have a nitrogen group with a valence of five are very poorly absorbed from the gastrointestinal tract. Only about 5 to 10 per cent of an orally given dose will be absorbed. For this reason it has been suspected by many of us that some of the variability of blood pressure response in patients seen from day to day on ganglionic blocking agents may be due to variations in response in absorption of the drug in the gastrointestinal tract. It was with great interest that we heard of a new compound which had a nitrogen group with a valence of 3 and which was completely absorbed from the gastrointestinal tract. This drug is called mecamylamine (Inversine). The average effective oral dose is 30 mg. per day or 10 mg. three times per day, which you see is much lower than that of the other ganglionic blocking agents, because it is completely absorbed. The disadvantages of mecamylamine are that the side effects are quite intense, particularly constipation. About 10 per cent of the patients develop atony of the urinary bladder with slowing of the urinary stream and frequency. However, in severe hypertension it produces as a rule the most uniform reduction of blood pressure. In those patients who develop atony of the urinary bladder or severe constipation we discontinue the drug and use other blocking agents.

Ecolid is another new ganglionic blocking drug. It has the longest duration of action which in some patients may be as long as 12 hours. In the majority it is about eight hours. It is poorly absorbed as are the others but because it is very potent the average effective dose by mouth is somewhere between 100-200 mg. per day in different patients.

Because of its long action it is necessary to give a smaller bed-time dose than with shorter acting blockers. Patients who are taking ganglionic blocking drugs are sensitive to these drugs in the morning and tend to lose their sensitivity as the day advances. The reason for this is not known but it is a fact that in most individuals the morning dose of a ganglionic blocker is usually about one-half the requirement of the afternoon, in order to keep the blood pressure evenly reduced throughout the day. The value of Ecolid is that with the exception of loss of visual accomodation it seems to have less side effects than the other blocking agents. It is an interesting fact that these drugs which are supposed to act in the same place, that is—to block all autonomic ganglia, exhibit these slight differences. Apparently some of them seem to act more intensely at some ganglia than at another. In all our patients that have difficulty with severe constipation or dry mouth with blocking drugs we use Ecolid. The visual accomodation can usually be taken care of with the use of glasses.

The technique of administering the ganglionic blocking agents spells the difference between successful and unsuccessful results. Certain precautions are required. If these are not used the results usually are poor. If carefully used, there is about a 90 per cent chance of obtaining a satisfactory reduction of blood pressure.

The first thing to recognize is that the dosage requirement varies widely from one individual to another, just as the dosage of insulin varies in a diabetic. In fact if you take the same attitude towards the use of a ganglionic blocking agent, as you take toward insulin you will understand how to use these drugs. With insulin it is necessary to give the dose that will clear the urine of sugar. Too large a dose will produce hypoglycemia and side reactions; too small a dose will leave the sugar present in the urine. It is necessary that the diabetic patient check his urine three times per day to see whether he is properly controlled. In the same manner it is necessary for the hypertensive patient to check his blood pressure three times per day to see if it is properly controlled. There is a little variation in the blood pressure from day to day requiring slight changes in dosage. What may be a therapeutic dose for one individual may be a toxic dose for another. Therefore, the physician must begin with a low dose and gradually increase to the effective level following the blood pressure very carefully.

The duration of action also varies somewhat from one individual to another so that one patient (just

as with insulin) may require two doses per day at 12 hour intervals; another three doses, another four and some only one. This can only be determined by seeing what effect the medication has on the blood pressure throughout the 24 hour period. Overdosage must be avoided as these are potent agents with uncomfortable side effects.

Two methods have been proposed for adjusting dosage. The method proposed by Dr. Smirk in New Zealand is to have the patient lie down for two hours after his medication, and then stand erect and motionless for a full minute. If during that period he develops faintness he knows that the dosage is too high and the patient reduces the dose to just below that level. This is to my mind an unsatisfactory method. The second method, which I have found to be more practical, is to have the patient or a member of his family check the blood pressure in the home.

A patient whose pre-treatment blood pressure was 220/150 was treated with a ganglionic blocking agent and hydralazine. His blood pressure was reduced to about 160/100 and he was discharged for home recordings of blood pressure. The recordings at home showed that the pressure was being nicely maintained at the lower level. He came into the office at the end of one week and his blood pressure as recorded in the office was 220/130. We had his wife who was taking the blood pressure check it in the office to see whether she was recording it properly. She was amazed to find that he had that high level and assured us that he was not getting that level at home. We had them bring in their apparatus. There was nothing wrong with the manometer nor with her method of taking the blood pressure. Again he went home and his pressures were uniformly lower and again he exhibited this spike of blood pressure when he returned to the office. This sequence happens to more than 50 per cent of our patients. If we had not had these home pressures as a guide we would have decided on the basis of the repeatedly high office blood pressure that the patient was no longer obtaining a satisfactory effect and that the dosage needed to be elevated. As a result the patient would have had disabling side effects resulting from overdosage and we would have discontinued the treatment as being a total failure. These results of home and office pressures in patients who have been treated with ganglionic blocking drugs have been confirmed in other centers. Drs. Corcoran and Page also have had exactly the same results with drug therapy. They find that the home pressures agree with the pressures obtained in the hospital under treatment and that they advise also that it is impossible and foolhardy to attempt to use ganglionic blocking agents unless the patient's blood pressure is being recorded three to four times a day in the home.

In addition there are certain factors that affect the sensitivity of the patient to the ganglionic blocking agents. We mentioned more sensitivity in the mornings and less sensitivity as the day wears on. The dosages have to be adjusted to take care of this. There also are seasonal variations. In hot weather the patient requires much less of the ganglionic blocking drugs than in cold weather. They usually must cut their dosages in half during hot weather. In September, October and November they are increased to the level required during the previous winter. Any acute or sudden salt loss will greatly increase sensitivity to the blocking agents. Diarrhea, vomiting, fever, sweating, mercurial diuretics, all of these can change the patient's sensitivity and necessitate the reduction of dosage for a few days until salt balance is restored.

Of less importance but occasionally seen in some patients, the ingestion of alcohol will greatly increase their responsiveness to the drug. However, in the majority of patients (and this is one of the compensatory features of the treatment) it is advisable that they have an ounce or two of whiskey when they return home from work. Patients who are on ganglionic blocking agents, usually note an additional reduction of blood pressure. I tell them to have a drink before dinner, which they like very much. Our treatment has some compensations.

QUESTIONS AND ANSWERS

Value of Ganglionic Blocking Agents in Predicting Results of Sympathectomy

Ganglionic blocking agents are of no value in predicting the results of sympathectomy. Furthermore, the response of the patients to an initial parenteral dose of ganglionic agents is no indication of how he will respond to prolonged treatment. Frequently we find that the most advanced cases of hypertension with uremia, due to renal disease are very sensitive to an initial small dose of ganglionic blocking drugs but on continued dosage they lose this and develop more or less complete tolerance. Therefore, it is not only of no value in predicting the

results of sympathectomy but it is also of no value in predicting the effects of prolonged treatment with ganglionic blocking agents.

Depression with Ansolysen

Suicidal depressions have not developed with any drug other than Rauwolfia. The question of tolerance is very real and some of it is connected with the seasonal change. Complete tolerance can develop to the ganglionic blocking drugs in the most severe cases. In such instances we must change the blocking drug. With the advent of other blocking agents on the market, I think when a patient develops complete tolerance it is a good idea to switch to one of these new agents. The cross tolerance is much greater in some of these blocking agents than in others. The method would be first to increase the dosage, to add other agents such as Rauwolfia and hydralazine, and if these are all unsuccessful change blocking agents.

Splanchnicectomy versus Sympathectomy

If I understand the question correctly you mean the extent of the removal of the sympathetic ganglia. I am not a surgeon, and am not qualified to answer that question. However, all I can do is repeat what some of my surgical friends have told me. Some do not agree with Grimson that the more extensive the sympathectomy, the greater the number of patients responding. There has been a school developed in recent years that one should begin with the single stage Peet splanchnicectomy as an adjunct to drug therapy. Many of these patients will respond and those who do not respond can be helped by drug therapy. I have no firm convictions on either one of these procedures.

The Indigent Hypertensive

Where is he going to find money to buy a blood pressure apparatus? We have many indigent patients in our clinic. Where does the indigent diabetic get his equipment? We have societies that supply them and I think that eventually we shall have, if necessary, societies that will provide blood pressure apparatuses. Our method has been to use our research funds to purchase about a dozen blood pressure apparatuses. We give out the apparatus to the indigent patient for a period of about a week so that we can get a week's record of his home pressures as a check on how he is doing. He then brings it back and it is loaned to another patient. (Our secretary handles all of this for us and keeps the records). These patients are unable to get their blood pressures recorded continuously but they do get a sufficient check so that we know where we stand. In private practice, I do not know what you could do. The Baumanometer people now make a blood pressure apparatus that sells for about $20.00.

The Sleeping Posture

Dr. Smith advises that the hypertensive patient be put in a position so that he can take advantage of the postural hypotensive effect of the drugs. He advises elevating the head of the bed so that the patient is in a semi-recumbent position. We have tried this. We find that in chronic therapy it does not make a great deal of difference from the supine position. If the patient has a marked postural hypotension, he seems to develop this primarily on standing up and that tilting at an angle of about 30 degrees succeeds only in making them uncomfortable. We do not utilize this method except rarely and seldom successfully when we do.

Thorazine

The question of its value as a hypotensive drug: I think that thorazine acts differently when given intravenously than when given orally and I don't doubt that intravenously administered it can be hypotensive. I do not think though, that if administered orally it is very hypotensive and I would not classify it as a hypotensive agent to be used in the treatment of hypertensive patients.

The Place of Sympathectomy

The statement that they respond better after sympathectomy than before is generally true. I quite agree, but I did say that we still use sympathectomy and I said that we use it in those patients who do not respond well to drugs either by reason of the fact that they cannot or will not cooperate.

Additional Salt

Does additional salt accentuate the blood pressure response as such? I know of no such evidence. I think that unless salt is restricted to a marked degree, no hypotensive effect is obtained. It is different in edema because edema decreases sensitivity to the ganglionic blocking agents and in those individuals moderate restriction is indicated. I would say that it would be very difficult to prove that moderate salt restriction has any effect.

Ulcer Patients and Rauwolfia

We have treated some patients with ulcers with Rauwolfia and I suppose that you are referring to the work done at the National Institutes of Health where they showed that injection of reserpine produces an increase in gastric acidity. However, the smaller doses of oral Rauwolfia have no effect on gastric acidity. We have seen bleeding peptic ulcers and also unexplained gastrointestinal hemorrhage in patients treated with Rauwolfia. On the other hand, we have had ulcer patients that have had no difficulty so I think that that is still an undecided question.

The Flicker Photometer in the Diagnosis of Hypertension

I must confess that I know very little about the Flicker Photometer and I don't use it, so I can't answer that question.

The Physiological and Anatomical Level of Blood Pressure under Treatment

I quite agree than one should not attempt to reduce blood pressure to normal but rather attempt to reduce the blood pressure to a level that the patient can tolerate. There are many patients particularly older ones with the

more severe grades of hypertension who develop lethargy, weakness, inability to concentrate, loss of ambition and deficiency of memory when their blood pressures are reduced to the normal level. They simply cannot tolerate such reduction. They apparently don't get sufficient blood flow to the brain. In those individuals it is much better to reduce the pressure to the levels they can tolerate. I would go along with your statement. The aim of treatments is to reduce the blood pressure as far as the patient can tolerate it towards normal. The physiological level of blood pressure therefore, would be the level at which this patient can function without signs of cerebral anemia. Therefore, the physiological level may not be the level that we customarily regard as normal.

Acute Pyelonephritis Becoming Chronic

Acute pyelonephritis can become chronic when there is an obstruction to the free flow of urine. Acute pyelonephritis frequently develops in the presence of obstruction to the free outflow of urine. Therefore, in all cases it behooves us to investigate and see whether there is such an obstruction.