CLINICAL CONFERENCE

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The Treatment of Hypertension with Modern Drugs

By Henry A. Schroeder, M.D. and H. Mitchell Perry, Jr., M.D.

DR. SCHROEDER: Most of us have been confused by the varying and conflicting reports in the literature and at meetings concerning the effectiveness or ineffectiveness of modern antihypertensive drugs and their place in the treatment of arterial hypertension. During the past five years we have been given a number of agents which appear to counteract to varying degrees the general vasospasm with which hypertension is associated, but all of which have produced toxic side effects or serious manifestations of their primary actions. The purpose of this conference is to attempt a clarification of the present situation in regard to such agents and similar ones being developed, and to consider when they should and should not be used. Perhaps it would be well to begin with a short resume of the pharmacology of the more important of them. Dr. Perry, you might discuss the Rauwolfia alkaloids, protoveratrine and its relatives, ganglionic blocking agents and hydralazine. That order, progressing from a central encephalic locus of action to a peripheral one at the vascular smooth muscle, is a good one. Let us confine ourselves to pure compounds.

DR. PERRY: The first three act primarily upon autonomic nerves. Reserpine, an alkaloid in the whole root of Rauwolfia serpentina, is a slowly acting corticohypothalamic depressant which produces partial nervous sympatholysis by inhibiting impulses to the sympathetic center. The extreme flatness of the dosage-response curve and the relatively weak action obviate the hypertensive episodes which complicate the use of other more potent vasoactive drugs. Unpleasant side effects include nasal obstruction, diarrhea, obesity, anxiety, nightmares and insomnia. Activation of peptic ulcers and colitis has been seen. Of much greater import, however, is an occasional extreme psychotic depression with suicidal tendencies. The limited antihypertensive effect may partially explain the failure to observe tolerance.

Veratrum alkaloids, of which protoveratrine is a purified principle, influence vasomotor centers in the medulla via the vagal and the carotid bifurcation receptors resulting in parasympathetic overactivity. They appear to stimulate the depressor nerves, thus causing a fall in blood pressure. The small margin of safety between therapeutic and toxic amounts makes dosage critical. The side effects are bradycardia, hypotension, nausea and vomiting. The rapid appearance of tolerance limits the ability of these agents to maintain continuous normotension.

Ganglionic blocking agents, of which hexamethonium and pentolinium salts are examples, diminish all nervous transmission at the autonomic ganglia. Their potency may initially produce acute hypotensive episodes which respond to a supine position. In general, the beneficial effects are those of sympatholysis, while the undesirable effects are those of parasympatholysis and include failure of visual accommodation, dry-mouth, constipation and difficulty with urination. The considerable tolerance, which is the rule when these agents are used alone, can be largely suppressed by combination with hydralazine. Apparently after a period of months, the effective dose becomes stabilized, even without the addition of an extra drug. They are quite rapidly ex-
creted and therefore must be given at regular intervals in order to maintain minimal variation in blood levels.

A PHYSICIAN: If your purpose is to block the sympathetic portion of the autonomic nervous system and many of the undesirable side effects result from tampering with the parasympathetic portion, why do you not use true sympatholytic agents?

Dr. Perry: Unfortunately with the known sympatholytic compounds, a dose, sufficient to produce an adequate hypotensive effect, is intolerable for any extended period, primarily because of tachycardia. Sufficiently potent new ones may be found which might replace the blocking agents.

Let us return to the pharmacology of hydralazine which is an extremely reactive chemical and a most valuable agent. Only a weak sympatholytic action can be demonstrated. It is quite rapidly altered in the body and probably undergoes more than one reaction. In vivo, hydralazine apparently binds sulfhydryl compounds since the combination can be isolated from the urine. In vitro, therapeutic levels of this drug combine with physiologic concentrations of pyruvate and other carbonyl reagents. Experimentally, it acts on constricted vascular smooth muscle. It is a true renal vasodilator; with its relatives, it has the unique property of increasing blood flow in the face of a lowered blood pressure. Isolated coronary arteries are also diluted. Our current ideas on its probable mode of action, however, involve the metal binding capacity of hydralazine, since it seems to have only this property in common with a group of non-neurogenic antihypertensive agents, such as azide, nitroprusside and thiocyanate. Since it can act as an antienzyme, perhaps an enzymatic reaction rate is altered by interference with metallic coenzymes, resulting in a changed irritability of vascular smooth muscle.

A PHYSICIAN: Do the other hydrazides, particularly the antituberculous agents, isoniazid and iproniazid, have similar metal binding powers and antienzyme activities?

Dr. Perry: They do. The relative strengths of their chelating capacities for the various transition metals is somewhat different for each compound. The antienzyme action of each also differs and may be quite specific.

There is no good evidence that the usually unequivocal but seldom dramatic antihypertensive effect of hydralazine is mediated via the central nervous system, although a central action has been demonstrated. It is a prolonged dilator, even on isolated vascular beds. Its antihistaminase activity, which may or may not involve a metal, partially explains some of the side effects, particularly, nasal obstruction and headache. In addition, tachycardia, anorexia, nausea and vomiting may occur. Tolerance is common when it is used alone, but seldom appears when a nerve-acting drug is added.

A PHYSICIAN: Sir John Parkinson recently quoted Sir Robert Hutchison as praying that we might be delivered "from inability to let well enough alone, from too much zeal for the new and contempt for what is old, . . . and from making the cure more grievous than the ill." How does this apply to the use of these potent agents whose distressing side effects you have just enumerated?

Dr. Perry: In effect, you would like to know the chance of helping the patient, the danger of hurting him, in either case, how uncomfortable are you going to make him for how long and, finally, whether there isn't a better way to do the same job. The new antihypertensive agents have been used in many ways by different investigators with varying results. Our experience in severe stages of the disease has been confined largely to an oral combination of hydralazine and methonium compounds. Those who wax enthusiastic about drug therapy claim that all elevated blood pressure can be reduced to normalcy with sufficient cooperation, perseverance and medication. Iconoclasts are skeptical both of such generalizations and of the value of whatever normotension is achieved. Beneficial effects of lowering blood pressure can be definitely established only for the small group of patients in the "malignant" phase of hypertension, as characterized by a mean diastolic pressure in excess of 130 mm. Hg, severe renal dysfunction and exudative and hemorrhagic retinitis with edema of the optic discs. Untreated, this syndrome is rapidly pro-
ggressive and almost always fatal within a year or two; whereas any treatment resulting in normotension and uncomplicated by increasing renal failure usually prolongs life and may restore the capacity to work. For the much larger group of patients with less severe degrees of hypertension, the statistical evidence, necessary indisputably to prove the value of treatment, is not yet available. Hypertension, however, is associated with a high incidence of vascular accidents, and our experience suggests that lowering the intra-arterial pressure diminishes such episodes in patients who have previously experienced one or more attacks.

As to the chance of harming the patient with drug therapy, it is very small if minimal precautions are observed. We have recognized no irreversible reaction to the drugs in the last 36 months and the rare prior cases occurred when control was poor and conditions of treatment not ideal. Hence we feel that permanent harm will not come to anyone who continues to take drugs under supervision. Discontinuation, on the other hand, may result in a rebound hypertension followed by vascular accident or progressive renal failure.

A comparison of the advantages and disadvantages of lowering an elevated blood pressure, per se, suggests that the value almost always outweighs the risk, since both increase proportionately to the severity of the disease. Undesired side effects, which plague all forms of treatment, increase the danger only slightly. With a combination of hydralazine and methonium therapy carefully administered, the overall hazard is small. Initially, drug-induced hypotension is not rare. Although alarming, this clinical picture must be sharply differentiated from shock, by the presence of peripheral vasodilatation and normal cardiac rate. In our experience, such episodes are transient; moreover, there has been no accompanying evidence of myocardial anoxia, and the syncope which accompanies cerebral ischemia responds readily to the supine position. No permanent damage, resulting from clot formation or oxygen deficit, has been observed by us in well treated patients. Drug-induced parasympatholyis may lead to obstruction of hollow viscera. Parasympathomimetic drugs, catheterization or even prostatectomy may be needed to control urinary retention in the male with prostatism. We have never seen paralytic ileus result from methonium therapy. With laxatives, an intelligent, cooperative individual can control his bowels, which pose the most stubborn and persistent problem. In particularly recalcitrant cases, gastrointestinal exposure to the autonomic blocking agent can be reduced by parenteral administration. The combination of constipation and renal decompensation leads to increased methonium absorption and decreased excretion, a condition which is self-perpetuating, since an accumulation of drug further reduces both gastrointestinal motility and glomerular filtration pressure. We treat the side effects as they appear.

Temporary discomfort can be expected after any considerable alteration in hemodynamics. For weeks or months after the initiation of drug therapy, considerable inconvenience is inevitable. The altered hemodynamics and the depressed nervous transmission are particularly marked for patients with severe stages of hypertension. Their blood pressures are very high and large doses of blocking agents are required. They, therefore, have all the symptoms of parasympatholysis plus anorexia and mental depression added to their woes. This would indeed be a high price to pay indefinitely for normotension, but fortunately the unpleasant side effects diminish and, except for masculine impotence, all finally vanish, although their complete disappearance usually takes many months.

A better way than this involved, sometimes unpleasant, and inconvenient method for the control of hypertension is needed, but none has yet been devised which consistently affects the severe stages of the disease. In reality, such therapy is no more complicated, inconvenient or dangerous than is the treatment of severe diabetes.

DR. SCHROEDER: Actually, the greatest dangers to life which we have encountered have involved cessation of therapy in severe and malignant stages. Forty per cent of patients in the former and all in the latter stages have died of the complications of hypertension, when therapy was stopped. These figures,
compared to total mortality rates of under 4 per cent for severe benign and 14 per cent for malignant stages treated adequately, enforce the implication that therapy, once begun, should be continued.

A PHYSICIAN: How do you feel about surgical sympathectomy of the Smithwick or Grimson types?

DR. PERRY: Adequate surgical sympathectomy unquestionably prolongs life when it lowers blood pressure, but it fails to relieve hypertension permanently in a majority of cases. For severely hypertensive patients who will not or cannot tolerate a satisfactory medical regimen, it is usually the only recourse. Sometimes its efficacy, like that of chemical sympathectomy, can be enhanced by hydralazine or restriction of dietary salt.

A PHYSICIAN: What about total adrenalectomy?

DR. SCHROEDER: To my knowledge, no one has yet been able to prove adrenal cortical overactivity in the majority of hypertensive patients. Certain persons appear to show its signs; in them, removal of the offending organ or suppression of its activity by specific antimetabolites is logical. When we can measure the overactivity chemically or functionally as we do in hyperthyroid states, we can then proceed logically and confidently. To remove an organ which is not directly involved in a disease process is hardly a fair therapeutic measure and may produce an equally bad, though different, disease. Of course, hypertension can be induced in animals by certain steroids and salt, but it does not follow that all hypertension in human beings is caused by steroids and salt. Similarly, despite the pandemic of experimental renal hypertension in laboratory animals, it does not follow that all human hypertension begins on a renal basis. The universality of human moderator-nerve hypertension is equally unproven. Human counterparts of each of these types of high blood pressure do exist, however, and it is likely that more than one influence-eurogenic, renal or adrenal—is operative in severe cases. Our diagnostic methods are not good enough yet to separate such influences. High blood pressure is only a sign caused by a variety of conditions and is not a disease in itself.

A PHYSICIAN: What is the right time to start treating hypertension?

DR. SCHROEDER: This is a difficult question to answer because the disease itself produces serious secondary pathologic changes at widely varying rates in at least three different organs. Increased intra-arterial pressure, sustained for many months or years, leads to cardiac hypertrophy and may progress to dilatation and failure; it leads to arteriolar nephrosclerosis which may terminate in diminished renal function and eventual uremia; and, most important, it apparently leads to an increased rate of progression of atherosclerosis. The eventual results are cerebral vascular accident, either hemorrhage or thrombosis, coronary arterial occlusion and other less common arterial accidents.

Obviously the right time to treat any patient is before irreversible damage is done. After damage has appeared it is still the right time to treat, in hope of preventing further pathology. Ideally, all patients should be treated when the blood pressure first becomes and remains elevated without symptoms or signs of secondary pathologic changes. An ounce of prevention is still worth a pound of cure. Unfortunately, modern drugs carry a certain risk of disability. They may produce side effects which are annoying to an asymptomatic individual; they may result in serious new diseases or, rarely, cardiovascular accidents for which the stage has already been set. The task facing any physician, therefore, is to weigh the risks of the disease against the hazards of therapy.

It is our practice at the present time to bring the blood pressure to normal by drugs, even in early stages of hypertension, realizing full well that late side effects or toxic reactions, now undisclosed, may become manifest in a few years. We watch patients carefully for such occurrences and any new and strange symptom is initially attributed to the drugs. We believe that treatment is mandatory when the "malignant" or accelerated stage of hypertension is present as previously defined. We believe that treatment is essential for prolongation of life.
when a patient has had one cerebral accident or congestive heart failure. In all other patients, treatment is elective, although in many it should be strongly urged. While it is true that a certain minor percentage of older individuals live to a ripe old age with sustained chronic hypertension, no one is able to predict the occurrence of cerebral vascular accident, heart failure or coronary occlusion. When it becomes possible to pick out those who will not have such accidents and in whom hypertension does not appear to be doing damage, they obviously should not receive treatment. Despite the statement that all patients with diastolic hypertension should be treated practically, they all cannot be at the present time.

A Physician: What drugs do you use to treat hypertension?

Dr. Perry: Considerable controversy continues about which drugs are the most effective and least distressing. In general, the more effective the agent, the more serious are the side effects. Ordinarily, we use one, two or three agents depending on the severity of the hypertension. If psychotic depression or agitation is not produced, reserpine benefits most patients. Although its hypotensive effect is usually slight for those whose blood pressure is labile and rarely elevated (except in a physician’s office), it is often sufficient to sustain normotension. The amount taken is not critical since a wide range of doses is effective without being toxic. For those with more severe hypertension and a normal blood pressure only during sleep, induced by heavy sedation, it is necessary to add hydralazine to achieve normotension. A hypotensive effect is usually obtained but is seldom abrupt; hence, the intake does not have to be finely adjusted. Relatively small quantities of the order of 250 mg. per day are used, since they generally suffice and since they obviate most of the delayed reactions. To lower fixedly elevated diastolic pressures, a ganglionic blocking agent is added to hydralazine and reserpine in a dose adequate to produce the desired result. The action of this drug is sufficiently dramatic that dosage must be carefully regulated. To minimize the wide fluctuations in blood pressure and also to prevent the very frequent tolerance to methonium compounds, it is often necessary to increase the hydralazine intake. Reserpine may lessene th required dosage of other drugs, even if alone it does not cause a significant change in blood pressure, and it frequently helps to correct methonium constipation. Perhaps the following case will indicate the method of therapy and the result achieved in severe hypertension:

L. L., a white male, was 34 years old when he was first seen in November, 1951 because of headaches for three months. At that time fundoscopic examination revealed hemorrhages and exudates without papilledema. His blood pressure was 250/140 mm. Hg and his heart was enlarged, although his lungs were clear and there was no pedal edema. He excreted only 5 per cent of intravenously injected phenol red within 30 minutes, and 2 plus albuminuria was present, without nitrogen retention. Hexamethion chloride every four hours by mouth was begun in increasing amounts until his supine blood pressure, which had not changed with hospital rest, fell to an average of 180/110 mm. Hg* with occasional readings of 140/90 mm. At that time, the size of his hexamethion dosage was made contingent on the level of his blood pressure. Oral hydralazine was then added and the fluctuations of blood pressure became smaller. He was maintained normotensive by 0.15 Gm. hydralazine, five times a day, with a simultaneous variable intake of hexamethion chloride as follows: 1 Gm. for any sitting systolic pressure over 140 mm. Hg, 0.50 Gm. for pressures between 130 and 140 mm. and 0.25 Gm. for pressures between 120 and 130 mm. He was then given a sphygmomanometer and taught to use it. After three weeks in the hospital, he returned to work immediately, although constipation, dry-mouth and some amblyopia persisted. Within two months he was free of symptoms. He has since continued his work as farmer and truck driver. About four years after beginning therapy, he is taking 0.10 Gm. of hydralazine and an average of 0.12 Gm. of hexamethion chloride, five times a day, to maintain an average sitting blood pressure of 150/92 mm. Hg. Although there are no visible lesions in his ocular fundi and his excretion of intravenously injected phenol red has increased to 12.5 per cent in 15 minutes, his albuminuria persists.

A Physician: Do you have any opinions on the relative merits of reserpine or protoveratrine as compared with the whole root of Rauwolfia serpentina or veratrum viride? Do you advocate combinations of drugs in the same pill?

* In this and subsequent mean levels of blood pressure, given in case reports, either 35 or 150 successive readings were averaged.
Dr. Schroeder: We have no strong opinions on the first question. The whole root of *Rauvolfia serpentina*, however, contains 14 alkaloids, among them yohimbine which is classed as a renal irritant and is said to be contraindicated in kidney disease. I know of no studies bearing on renal irritation due to the whole root, but I prefer not to use it extensively until absence of irritation has been shown. Pure compounds are usually better to use in the long run than are mixtures, if the effects desired are produced as well as by the crude material. Protoveratrine, properly administered, can be a very useful drug in those patients unable to take ganglionic blocking agents. By combining effective hypotensive doses with hydralazine, relatively even control of blood pressure is often seen, impossible to achieve with either drug alone. Apparently, the mixture of protoveratrine A and B represents the active hypotensive (and emetic) principle of crude preparations. A study made in our clinic several years ago by Gropper, Surtschin and Hedrick on a partly purified material was disappointing.

In answer to the second question, we never use combinations of drugs in one pill. The practice of combining two drugs with different actions is illogical. The dose of one may be constant and that of the other, variable. Reserpine requires a constant dosage which must usually be reduced in time. The ganglionic blocking agents need variable doses. Protoveratrine needs a dose different in the morning from later in the day. Hydralazine is usually constant but varies from patient to patient. Putting any two into one pill would require large numbers of different combinations with varying strengths of each. Nor do we advocate the "baked Alaska" pill, in which two counteracting drugs, such as a stimulant and a depressant, are combined. These supposedly convenient aids assume that all men and their dysfunctions are alike.

A Physician: In what percentage of patients does hypertension persist despite drug therapy?

Dr. Perry: In our experience, no patient has initially proved totally resistant to combined hydralazine and methonium compounds. In fact, the blood pressure of any untreated cooperative patient can be brought down to normal with the adequate use of drugs and maintained there indefinitely, if it seems desirable. Sometimes the dosages required are very large. Of course, in the presence of sufficient renal damage, one must be satisfied with merely moderating the hypertension, since normotension is incompatible with adequate glomerular filtration and therefore with life. Occasionally considerable tolerance occurs in patients who have begun therapy and then discontinued it. Such patients require much larger quantities of drugs for control each time treatment is reinstituted. The following case is the most striking example of this phenomenon that we have observed and represents the only instance when we were unable to affect human hypertension by a combination of oral hydralazine and autonomic blocking agent. It also illustrates the good results that can be achieved in the face of azotemia and the dramatic disappearance of cardiac failure as an elevated blood pressure is lowered.

J. M., a Negro man, was 39 years old when he was first seen in December, 1953. His obvious dyspnea had gradually increased during the previous year. His blood pressure was 246/148 mm. Hg. Hemorrhages, exudates and papilledema were evident in both ocular fundi. Examination of his chest revealed basal rales and marked cardiomegaly. Azotemia was not present and the excretion of intravenously injected phenol red was 18 per cent in 15 minutes, but there was 4 plus albuminuria. Since hospital rest failed to alter the hypertension significantly, oral administration of hexamethonium chloride was begun. Within 72 hours his blood pressure fell to 150/90 mm. Hg and, simultaneously, the rales in his chest disappeared. Although his intake of drug was only 1 Gm. per day, he refused further therapy because of nausea, distention and asthenia.

Six months later, he was readmitted to the hospital after digitalization failed to control severe respiratory distress, anasarca, and oliguria. To his previous abnormal physical findings, which had persisted essentially unchanged, were added bilateral pleural effusions, a diastolic gallop rhythm, hepatomegaly, ascites and bilateral pedal edema. The formerly normal nonprotein-nitrogen level had risen to 71 mg. per 100 ml. of blood. He now agreed to oral pentolinium therapy. The dose was gradually increased to an average of 2.5 Gm. per day in divided doses before his blood pressure fell to normal levels again. With normotension, heart failure quickly vanished. To allow adequate renal filtration, his blood pressure was maintained at a
compromise level of 170/110 mm. Hg. The non-protein-nitrogen value immediately before discharge from the hospital had decreased to a normal 27 mg. per 100 ml. of blood and he was sent home with an average daily dose of 1 Gm. each of oral hydralazine and pentolinium tartrate.

For four months he took approximately this amount of medication regularly and then was able to return to work; his mean sitting systolic pressure was 155 mm. Hg. Feeling that he was cured, he then discontinued treatment. His final readmission was 43 days later. Again he was in marked respiratory distress. His blood pressure was 200/140 mm. Hg. Fundoscopic examination revealed blurred optic discs without frank papilledema, but there were fresh hemorrhages and exudates. The signs of cardiac failure were more marked than on previous hospital entries. The nonprotein-nitrogen level was 105 mg. per 100 ml. of blood. An attempt was made to recontrol his blood pressure with hydralazine and pentolinium tartrate by giving increasing parenteral doses. After 4 Gm. of pentolinium tartrate and 2 Gm. of hydralazine within a 24 hour interval had no significant effect, he was given 0.5 Gm. of each intravenously in the same syringe during a period of three minutes. The resultant fall in diastolic pressure from 145 to 130 mm. Hg lasted only for seven minutes. Thereafter his uremia rapidly progressed and he died of renal failure two weeks after hospitalization.

Dr. Schroeder: One sees reports in which patients were alternatively given placebos and these drugs. The usual result of such studies has been to indicate that the drugs are relatively ineffective. We have noticed the same phenomenon ourselves when the drugs were discontinued or when placebos were used. I know of no better way to produce tolerance than to give these agents intermittently. It is essential to therapy to apply even continuous therapeutic pressure, increasing to the point where the desired results are achieved without intermittency or periods of discontinuation. This phenomenon is not at all understood but it may be likened in a broader sense to that of bacterial resistance to chemotherapeutic agents used intermittently in an infection. There appears to be something about normotension, when achieved with these drugs, which carries with it a favorable outcome insofar as the continued action of the drugs themselves is concerned. Two, three or even many times the original dose may become necessary when patients are taken off and put back on. One of the most prevalent factors in producing this curious kind of tolerance to the agents lies in the insecurity of the physician when he first sees the blood pressure falling to normal levels from very high ones and the patient has symptoms associated with this fall. He then becomes worried and discontinues the drug; the blood pressure soon returns to its previous levels and he finds it extremely difficult to control the hypertension from then on. On the other hand, we have not observed tolerance developing when these drugs were properly used and normotension or a reasonable facsimile thereof was achieved for long periods of time in a fresh, untreated case.

Dr. Perry: In fact, we have observed quite the reverse. Eventually, there is a significant diminution in the quantities of hydralazine and methonon compounds needed to maintain a normal blood pressure. For instance at the end of the first year of treatment, 79 unselected patients who had maintained diastolic pressures below 100 mm. Hg with these two drugs alone took only 73 per cent of their initial doses of blocking agent; at the end of two and three years the required percentages were 57 and 46, respectively. The diminution in hydralazine intake was only slightly less. A few have been able to discontinue drugs entirely, while some are controlled with reserpine alone and some with a combination of reserpine and hydralazine. In striking contrast, patients whose diastolic pressures consistently exceeded 100 mm. Hg for one reason or another continued to use approximately their original doses of both agents to maintain even their inadequate blood pressure control. The following case illustrates the steadily decreasing amounts of antihypertensive agents needed to produce successively longer and more complete remissions of hypertension.

A. R., a white woman, was 34 years old at the time she first entered Barnes Hospital in October, 1951 with a 12-year history of an infected kidney. Physical examination was not remarkable except for a few hemorrhages without exudates or papilledema in the ocular fundi, a blood pressure of 240/120 mm. Hg, and cardiomegaly. There was no albuminuria; the excretion of intravenously in-
jected phenol red was 25 per cent in 15 minutes; but intravenous pyelography suggested right pyelonephritis. With a daily 0.5 Gm. hydralazine and 3.0 Gm. hexamethonium chloride, her blood pressure quickly fell to an average of 140/90 mm. Hg. She was discharged from the hospital with this maximum dosage to be taken according to our usual regimen in which the amount of blocking agent is determined five times a day by reading the sphygmomanometer. Within a month the side effects of therapy had disappeared and she was leading a normal life. Gradually and automatically her hexamethonium intake decreased along with her blood pressure, and by September 1952, she only required 0.25 Gm. per day since her sitting systolic readings were almost invariably less than 130 mm. Hg and frequently below 120 mm. By this time we had reduced her daily dosage of hydralazine to .05 Gm. With cooler weather, however, her blood pressure rose to 150/100 mm. Hg, thus automatically increasing her mean hexamethonium requirement to more than 1 Gm. per day. By April of 1953, she needed no further hexamethonium ion. Shortly thereafter hydralazine was also discontinued. After an interval of three weeks her normal mean systolic pressure slowly rose to 155 mm. Hg, reaching 180 mm. on one occasion. Subsequently, small amounts of reserpine rapidly reduced her blood pressure to 125/75 mm. Hg. After discontinuation of this alkaloid, normotension persisted for two months without any antihypertensive agents. When it again increased a briefer course of reserpine was followed by a more extended period of strict normal blood pressure with no drug intake, which has continued seven months to date.

A PHYSICIAN: You mentioned some evidence that treatment of severe hypertension prolongs life and avoids disability. Would you elaborate?

DR. PERRY: The "malignant" stages of hypertension as previously defined are uncommon, but they serve to show the efficacy of therapy. Several series of patients with such an accelerated phase of the disease have been followed, indicating the dire prognosis without treatment. In the most recent compilation, Schottstaedt and Sokolow found that in the absence of therapy the average life expectancy was nine months, with almost half of the subjects succumbing in 90 days and only 15 per cent surviving for two years. Before effective drugs were available, Smithwick demonstrated a significant reduction in mortality among patients subjected to surgical sympathectomy as compared with a similar unoperated group. More recently, Smirk has shown a similar improved prognosis following treatment with autonomic blocking agents alone. Among 64 of our patients who were initially in the "malignant" stages of hypertension and who have regularly taken oral hydralazine and hexamethonium chloride over a two to four year period, 54 are alive and 51 are back at gainful occupations. It is difficult to see how such figures can be discounted or how a case history like the following can be ignored.

I. M., a Negro woman, was 47 years old when we first saw her in August, 1951. Two years previously she became totally incapacitated by intermittent but increasingly severe bouts of left ventricular insufficiency; and three years before that, she was denied life insurance because of albuminuria and hypertension. When she entered Barnes Hospital, she had long been unable to lie down, despite salt restriction and full digitalization. Fundoscopic examination revealed hemorrhages, exudates and papilledema. The other significant physical findings included bilateral pleural effusions, cardiomegaly, hepatomegaly and pedal edema. Her renal status was defined by 2 plus albuminuria, a normal blood nonprotein-nitrogen level, and 5 per cent excretion of intravenously injected phenol red in 15 minutes. Hydralazine and hexamethonium therapy according to the usual regimen dramatically lowered her mean blood pressure to less than 140/90 mm. Hg, where it remained for two years during which she regularly took her medication. During this interval, she was entirely free of symptoms including side effects of the drug and she daily worked 8 to 10 hours in a restaurant. Her ocular fundi became grade I (Keith-Wagener), her albuminuria disappeared and her cardiac size reverted to normal. Despite discontinuation of her digitalis and salt restriction, there was no recurrence of heart failure and she was accepted for insurance by the company which had rejected her seven years earlier. Unfortunately, she has since become careless in following her dosage schedule with several resultant bouts of hypertension which have been incompletely controlled by increased amounts of drugs.

A PHYSICIAN: How about cerebral vascular disease even when the blood pressure is adequately controlled?

DR. SCHROEDER: There is no tendency to cerebral hemorrhage when the blood pressure is well controlled. Cerebral thrombosis, on the other hand, can probably occur when normotension is induced too fast. When we began to use antihypertensive drugs, we saw three such episodes in patients whose blood pressures were
being rapidly brought down to low levels for the first time. We have not had another for several years. The statistics to date are inadequate to indicate whether or not cerebral thrombosis is prevented. In our series no thromboses have developed in patients who were well treated, even though such accidents may have occurred before treatment. When cerebral vascular disease is diffuse with mental deterioration, we have seen no improvement. The control of excessive vasospasm merely allows nature to take its course without the insult of hypertension.

**A Physician:** What about the effect of treatment on the course of atherosclerosis?

**Dr. Schroeder:** It is too early to tell. Blood cholesterol levels usually fall rapidly and remain lower for years in most patients taking hydralazine. What this means, we do not know. Angina pectoris usually gets better but occasionally becomes immediately worse, probably on a hemodynamic basis. When we can diagnose atherosclerosis for sure in its beginning, we may be able to judge the effects of treatment on this phase of the problem.

**A Physician:** Heart failure is reported to account for over half of the deaths in patients with sustained hypertension. Is the treatment of hypertension of value in the presence of this complication?

**Dr. Perry:** Heart failure has almost disappeared as a cause of death in our series of patients. A failing left ventricle can be dramatically relieved by parenteral autonomic blocking agent, provided that elevated blood pressure contributes significantly to the cardiac load. This is true, regardless of the other contributing causes of the heart failure. Such relief is gratifyingly permanent in that only a handful of our previously digitalized patients treated with oral hydralazine and methonium compounds continue to need digitalis. Some of these points are illustrated in the fourth case history.

**A Physician:** What limitations does azotemia or uremia place on drug therapy?

**Dr. Perry:** Slight azotemia is compatible with an excellent clinical result. On the other hand, lowering the blood pressure in the presence of unequivocal uremia only hastens the certain demise. We have found drug therapy useful, if the nonprotein-nitrogen level on admission to the hospital does not exceed 60 to 75 mg. per 100 ml. of blood. A nonprotein-nitrogen level much greater than 100 mg. per 100 ml. indicates so much renal damage that any diminution in glomerular filtration pressure often quickly proves fatal. The efficacy of treatment in the intermediate group depends upon many factors, including the intelligence and cooperation of the patient as well as the ability and perseverance of the physician. Although we have not produced nitrogen retention where it did not previously exist, it is usual for azotemia to be temporarily worsened as the blood pressure falls. With severe renal insufficiency, it is necessary to compromise and forego strict normotension. It must be remembered that methonium compounds are apparently not metabolized in the body; whatever is absorbed must be excreted by the kidney. Renal decompensation may convert one-half to one-eighth of the usual therapeutic intake into an effective dose. There is no known contraindication to using hydralazine in the presence of azotemia. The sole function of antihypertensive drugs is to lower blood pressure. They prevent further ravages of hypertension, but they do nothing to heal damage already produced. Nonetheless, after a period of months or years of lowered blood pressure, there is an unexplained and not inconsiderable improvement in renal function. The following case report shows how skill and infinite patience on the part of a house officer controlled the blood pressure of an azotemic patient in a range high enough to allow adequate glomerular filtration and low enough to control the heart failure from which he suffered.

H. M., a Negro man, was 50 years old when he was first admitted to Barnes Hospital in August, 1953. Although hypertension had been recognized three years previously, symptoms had begun six weeks before entry with the appearance of paroxysmal nocturnal dyspnea, ankle swelling, anorexia, nausea, vomiting and a weight loss of 15 pounds. Fundoscopic examination failed to reveal hemorrhages, exudates or papilledema. There were rales in the bases of both lungs, and clubbing of the fingers and toes was present without cyanosis. His blood pressure was 210/130 mm. Hg and his heart was enlarged with a diastolic apical murmur and a presystolic gallop. Hepatomegaly and pedal edema were noted. The abnormal laboratory data included 2 plus albuminuria and a nonprotein-
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nitrogen level of 63 mg. per 100 ml. of blood. In view of his limited intelligence, the presence of azotemia, and the absence of the ocular stigmata of "malignant" hypertension, only digitalis, dietary salt restriction and reserpine were prescribed.

He was readmitted after seven weeks because of reappearance of both right and left ventricular failure. The changes in his physical examination were confined to the ocular fundi and included hemorrhages, exudates and papilledema. The only significantly altered laboratory finding was a non-protein-nitrogen level of 109 mg. per 100 ml. of blood. Cautiously given hexamethonium chloride resulted in a fall in his blood pressure from its admission value of 240/140 to 190/115 mm. Hg. There was an immediate improvement in the signs and symptoms of cardiac decompensation and a concomitant rise in his nonprotein-nitrogen to 160 mg. per 100 ml. of blood. Maintenance of this blood pressure for a few days was accompanied by a fall in the azotemia to its admission level. Therefore the blood pressure was further slowly lowered to 170/100 mm. Hg and this was followed by a second increase in the nonprotein-nitrogen level to 125 mg. per 100 ml. which then gradually declined to less than 50 mg. where it remained. At the same time the last evidences of cardiac failure vanished. After almost two months of hospitalization, he was discharged with this minimal azotemia and compromised blood pressure. His medication was taken by mouth five times a day and consisted of a constant dose of 0.10 Gm. hydralazine and a simultaneous variable dose of hexamethonium chloride averaging 0.49 Gm. Unfortunately he discontinued his regimen because of absence of symptoms and a month later died of cardiac failure, a few hours after his final readmission to the hospital.

A Physician: You said you had never seen a patient really resistant to these drugs. That may be so, but what is your actual experience, taking into account all of the factors involved, cooperation, side effects, late toxicity, etc.?

Dr. Perry: On the whole, it is good. About 80 per cent of our patients with severe hypertension control their systolic pressures at levels of 160 mm. Hg or below in four readings out of five. Few patients who need treatment cannot be encouraged by the physician to weather successfully the initially rigorous regimen and achieve lasting benefit. Private patients fare better than ward ones, and white patients better than Negroes. We do better than house officers, perhaps because we persist in treatment and handle side effects as they appear. We have an impression that the hardest therapeutic problems, barring azotemia, occur in men from 40 to 60 years old with "benign" hypertension and tortuous aortas. The next most difficult are the women with extreme emotional lability; partial autonomic blockade does not prevent spikes of blood pressure, induced by emotion and troughs, following relaxation; reserpine helps. A comparatively easy problem is the young "malignant" hypertensive without nitrogen retention.

A Physician: Although there are some reports of very favorable results following these drugs, there are many who feel that drug therapy has little to offer hypertensive patients. Can you explain this discrepancy?

Dr. Perry: The conflicting reports regarding these drugs are disturbing. First, however, the areas of agreement should be emphasized. Although different investigators have used different drugs in different ways, those who have used them in adequate doses and according to logical schedules agree that the progress of severe hypertension has been halted or markedly retarded in many cases. As has been previously discussed, our definite claims of prolonging life have been confined to that small group of patients with "malignant" hypertension and a desperate immediate prognosis. I know of no contrary claims by an investigator using similar dosages for similar patients. Beyond the area of agreement, there are considerable areas of disagreement as to the efficacy of medical therapy. Several factors must be jointly responsible for the differences of opinion. The difficulty in evaluating the severity of human hypertension is not to be underestimated. Many physicians who do not believe in antihypertensive therapy insist that its good results are found only in those patients who are mistakenly classified as having bad hypertension. When a physician’s skepticism as to the value of therapy is combined with an excessive fear as to its potential risk, he usually resorts to doses of insufficient size and frequency. This is unfortunate, since partial treatment often has no significant effect, and yet antihypertensive agents are commonly abandoned on the basis of such an inadequate trial. Unjustified expectations by the patient may be at fault. Many are not helped by drugs.
because they expect too much and hence they are unwilling to tolerate temporary unpleasant side effects. Too many physicians are alarmed to see a sphygmomanometer in the hands of the public. Whatever the theoretic disadvantages of giving a blood pressure machine to a patient, the dangers of not doing so are very real. Ganglionic blocking agents are potent drugs. Sufficient must be given to achieve the desired antihypertensive effect, but hypotension-producing excesses should be avoided. The most satisfactory way to do this on a chronic basis involves giving the patient a sphygmomanometer and teaching him how to use it. We were fortunate in first giving the combination of hydralazine and hexamethonium chloride to four "malignant" hypertensive subjects, including the subject of the fourth case report, who were obviously rapidly deteriorating. To see three of these leave the hospital and return to gainful occupations was sufficient to counteract several succeeding failures.

A Physician: Are patients not made neurotic when they are taught to determine and record their own blood pressures?

Dr. Perry: I have never seen a patient, who had achieved normotension, made nervous or neurotic by taking his own blood pressure, although I have seen a few who became tired of the routine and stopped it. The situation seems analogous to a diabetic testing his own urine. Elevated blood pressure is not alarming when it can be rapidly and safely lowered to any desired level. In fact, observing an elevated pressure fall following a pill instills a sense of security. It is true, of course, that they become as "blood-pressure conscious" as are diabetics "sugar conscious."

A Physician: What type of patient would you not treat with these modern drugs?

Dr. Schroeder: There are probably only three types of patients who do badly. The first is the uncooperative individual who refuses to take pills at stated intervals and who will not or cannot learn to take his own blood pressure. When the disease is serious or in "malignant" stages, giving potent drugs intermittently and ineffectually is tantamount to allowing rapid progression with eventual fatal outcome. In such cases, one has recourse only to surgical sympathectomy in an attempt to prolong life.

The second kind of patient is the one with severe azotemia. We have 16 individuals with moderate nitrogen retention who are alive after three years; however, when frank uremia or marked azotemia is present, these drugs are almost valueless. Although they may relieve the workload of the heart and avoid pulmonary edema, the inexorable course of the disease is not halted. Whenever nitrogen retention is present, it is possible to lower the blood pressure beyond the point where adequate glomerular filtration through damaged kidneys can occur.

In such situations, particularly after cardiac decompensation has occurred, it may be difficult to steer between the Scylla of heart failure and the Charybdis of renal failure, but by careful attention to detail it can be done. The third kind of case which should not be treated is the person with systolic hypertension on an atherosclerotic basis who has a normal diastolic pressure. These drugs act merely on excessive vasospasm. They do not act on hard pipes. Atherosclerotic individuals with a blood pressure of say 200/80 mm. Hg may achieve a blood pressure of 140/30 mm. Hg, but such a hemodynamic situation is hardly compatible with a good state of health. We are treating vasospasm and thereby affecting the general health of the patient. We are not treating a number.

A Physician: What kind of patient is apt to respond to reduction of sodium in the diet?

Dr. Schroeder: In our experience the best responses to sodium reduction are in women with central obesity, some disturbance of their generative organs, a history of a rapid gain in weight and low sodium or chloride concentration in sweat. So far nine of these women have come to autopsy or have been operated upon, and all but one have shown adrenal cortical adenomata; the other had pituitary basophilia. These patients apparently form excessive amounts of salt-retaining hormone and may represent a variation of primary aldosteronism. In general, we use hydralazine and methonium compounds since they do respond to these drugs, although some appear resistant at first. We, therefore, rarely need sodium restriction in them.
A Physician: Why do you not use sodium restriction in all cases?

Dr. Schroeder: Not only is it very inconvenient for the patient but there may also be an element of danger to it. When hydralazine is being given restriction of sodium in the diet may result in the "low-salt syndrome" or salt depletion in some patients. Apparently, hydralazine is a salt losing agent for kidneys that already show a tendency to lose salt, as hypertensive kidneys may. We have seen sodium depletion occur often enough to be thoroughly aware of its dangers when hydralazine is being employed.

A Physician: What about the treatment of hypertension in pregnant women?

Dr. Schroeder: I think that these cases must be divided into two types. First, in hypertensive women who become pregnant there is no contraindication to treatment. We have had very little experience with pregnancy in previously hypertensive women who were on these drugs, inasmuch as most of our patients are in the older age groups. For example, we have seen one patient who had two miscarriages in the past, who delivered a stillborn infant at six months, later delivered a premature but normally developed infant who lived for about 30 hours and is now pregnant again. So far no surviving babies have been born to pregnant women taking these drugs under our care. The second type of case is that in which toxemia of pregnancy appears. In such situations antihypertensive drugs may be lifesaving, lowering the blood pressure to reasonable or normal levels and allowing regression of the secondary effects of cardiovascular and renal strain. Patients can be carried in such situations until either delivery or operative intervention.

A Physician: You mentioned delayed toxicity from some of these agents. Could you be more specific?

Dr. Perry: Two separate clinical entities have been reported, one resulting from hydralazine and one from hexamethonium chloride. The first occurs in about 10 per cent of patients who take 0.5 Gm. or more of hydralazine daily for at least six months. It is rare when smaller amounts are ingested. At its mildest, the syndrome consists of arthralgia and laboratory findings, usually associated with hepatic disease; in severer forms, it simulates acute rheumatoid arthritis; while the fully developed picture is indistinguishable from disseminated lupus erythematosus. Confirmation of the diagnosis is obtained from the elevated cephalin-cholesterol flocculation and thymol turbidity of the serum. Fortunately the process is reversed when the offending drug is stopped. No permanent sequelae have persisted and no fatalities, except those resulting from the recrudescent hypertension have been observed.

Hexamethonium toxicity is much less frequent and well defined. Pathologically it is characterized by a peculiar interstitial fibrosis of the lungs. We have only observed it in azotemic patients with the "malignant" stages of hypertension. It, too, apparently follows an extended and larger than average drug intake. It is recognized clinically by extreme tachypnea with surprisingly few concomitant pulmonary symptoms or signs. Breathing is characteristically improved, not worsened, by the supine position. Roentgenograms of the chest have been confusing and led to varied diagnoses. For the last 30 months we have not recognized this syndrome clinically, perhaps because of greater skill in using autonomic blocking agents.

A Physician: Your remarks on toxicity disturb me. How can I avoid it in my patients? Do I have to watch them at very frequent intervals?

Dr. Schroeder: It is relatively easy. If one examines patients at three-month intervals and advises them to watch for the warning signs of arthralgia, which usually bring a patient to a physician anyway, and then tests for the cephalin-cholesterol flocculation or the thymol turbidity of their blood, one can pick up "hydralazine disease" before it becomes advanced. Reducing the dose of hydralazine to small quantities or omitting it entirely will cause rapid reversal of symptoms. Our largest problem is in those patients who cannot take hydralazine and whose hypertension has recurred in spite of the use of large or even abnormal doses of ganglionic blocking agents and reserpine. One can avoid the toxic reactions of the ganglionic blocking agents, particularly the interstitial pneumonia, by treating the patient...
adequately: in other words, by controlling the blood pressure well and not allowing wide swings to occur. A follow-up of the patient at three to six-month intervals is usually enough to avoid these uncomfortable and distressing reactions. However, in the treatment of hypertension, as in the treatment of diabetes, the patient must be educated both as to the actions of the drugs and to the disease itself in order that he may intelligently manipulate his therapy and achieve a return to a state of health desired by treatment of any chronic disease. It is our impression that physicians are either too fearful of these drugs or are not concerned enough with their primary actions and use them without respect for their potency. A happy medium between a knowledge of hypertension and knowledge of the drug is essential. I believe that any physician who can treat and control severe diabetes can treat and control hypertension with modern agents.

A PHYSICIAN: Why don't we use the mildest acting and safest drugs in all cases and avoid risk?

DR. PERRY: Because the aim of treatment is to achieve normalcy. To give reserpine alone or a low salt diet to a patient rapidly advancing into uremia is similar to treating diabetic coma with diet or pneumonia with cupping. Mild cases need only mild drugs; severe cases require the most potent ones in doses large enough to produce the effect desired. We must use everything we have to stop the process, and use our heads when we do it.

A PHYSICIAN: What is the rationale for combining ganglionic blocking agents and hydralazine? It seems to me that some reports on the use of hydralazine alone were disappointing, while some people were optimistic about ganglionic blocking agents used alone.

DR. PERRY: We use both because in our hands the combination has proved the most effective therapy available. It is true that hydralazine alone frequently does not lower blood pressure significantly and only rarely produces normotension. On the other hand, although ganglionic blocking agents by themselves almost always lower blood pressure initially, control is usually very irregular and tolerance seldom fails to develop quickly. Having frequently observed the initially successful therapy become increasingly less valuable, we searched for a possible explanation. The most reasonable suggests that after human hypertension has exceeded a certain degree of severity, it is rarely of purely neurogenic origin. Ordinarily, there is a renal component as well. Our present concept is that hydralazine counteracts the renal factor, whatever it may be; whereas ganglionic blocking agents affect the autonomic nervous system, or neurogenic factor.

DR. SCHROEDER: Hydralazine is a unique drug with several fundamental actions about which we know very little. Dr. Perry has discovered that some of the antihypertensive agents not acting on nerves inhibit dihydroxyphenylalanine decarboxylase, an enzyme which contains pyridoxal phosphate and presumably a trace metal. Furthermore, hydralazine enhances the action of monamine oxidase, a property shared by some other chelating agents. It is possible that the drug may affect certain enzyme systems concerned in the relief or prevention of excessive vasospasm. Further to stimulate our imagination, there is a substance, described some 15 years ago, which we named pherentasin. It is a long-acting vasoconstrictor substance procured from human hypertensive arterial blood. To date it would appear to be a primary amine, possibly a polypeptide. We have recently been able to detect its presence in small amounts of venous blood by using a spirally cut rabbit's aortic strip suspended in oxygenated Krebs-Ringer solution. A sustained constriction occurs when pherentasin is added to the water bath. This substance has certain peculiarities in regard to trace metals and metal binding agents. In the first place, its activity is completely destroyed by such compounds as hydralazine, thiocyanate, ethylenediamine tetraacetate, 8-hydroxyquinoline, nitroprusside and sodium azide, all of which show some antihypertensive properties in man or in animals. Furthermore, manganous ion is the only metal tested that destroys pherentasin in vitro. When this substance is demonstrated in the blood of hypertensive patients and their blood pressures are then controlled with hydralazine, the substance can no longer be found. Because extraneous metals have been found in
human kidneys and urine, we speculate that some nonessential metal is inhibiting a metalloenzyme in the kidney, the nature of which is unknown but which is concerned in the alteration of intermittent vasospasm into permanent vasospasm and eventually produces organic changes in the kidney which maintains the blood pressure high. Hydralazine attacks that mechanism. These are our ideas to date and the use of two differently acting drugs appears logical in their light.

A Physician: You mentioned previously that after a long period of therapy some of these patients can take considerably less drug than at first. Dr. Wilkins, in his recent article in the Journal of Chronic Diseases, implies the same. Do you actually believe that the basic process of hypertension is being reversed?

Dr. Schroeder: We do. The evidence is not yet conclusive but it appears from the clinical measurements that one can make that the underlying process is reversing itself very slowly in well treated patients. It also appears that the underlying process is not reversing itself in partly treated patients. Those whose blood pressures are well controlled eventually need only a fraction of their original dose of drug or perhaps need only a small amount of reserpine whereas two to three years previously they had required large doses of ganglionic blocking agents, reserpine and hydralazine, to achieve control. Those individuals have shown an improvement in the electrocardiogram often to normal, a diminution in the size of the heart, which comes very slowly after two years or more, and, what has been more striking, an improvement in renal function toward or to normal, a totally unexpected finding. The evidence is accumulating that the secondary effects of hypertension are changing in the direction of normal and, possibly, that the underlying disease process itself is slowly reverting to a normal state in that less and less of the drug is being required.

A Physician: Would you elaborate on your ideas regarding the etiology and pathogenesis of hypertension in the light of the primary actions of these drugs?

Dr. Schroeder: While it has not yet been adequately proven that the sympathetic nervous system is overactive in arterial hypertension, three of the four types of drugs which have been mentioned act upon the autonomic nervous system. While it is possible that a normal tonus of the sympathetic nervous system is present in hypertension, the evidence is to the contrary. We have not time to list the evidence which, although indirect, points to overactivity. Let us say, then, that certain persons in the population have the ability to react to stress by vasospasm, either because of inherited or developmental traits. These persons may show a positive cold pressor test even though they are normotensive. As has been well worked out by Hines, many of them develop hypertension 10 or 20 years later. If this is so, a certain proportion of the population is predisposed to hypertension. It is only through nervous mechanisms that these reversible reactions can take place and one must assume that the sympathetic system plays the major role. Now the crux of the whole matter of pathogenesis, the "64 dollar question," seems to be: What factor or factors convert temporary intermittent vasospasm into permanent vasospasm? From epidemiologic studies, it would appear that there may be something in our civilization which tends eventually to convert reversible neurogenic vasospasm into irreversible or permanent vasospasm. In view of the tremendous amount of work on the kidney and its relation to sustained hypertension in animals and man, our suspicions are naturally directed to that organ. However, it has been shown conclusively, both experimentally and clinically, that organic renal arteriolar disease follows and does not precede the development of chronic hypertension. In dogs, the lesions may not appear until the fourth or fifth year of sustained hypertension. Therefore, we cannot implicate an organic renal basis. What other basis is there? We may look upon certain renal enzymatic mechanisms as being possibly affected by some exogenous material in civilized areas. Our suspicions became naturally aroused when it dawned upon us several years ago that all of the agents used to treat hypertension had in common only the ability to bind trace metals. Hydralazine was found by Dr. Perry to do this; thiocyanate is a commercially useful material for purification of
ores; nitroprusside, 2,3-dimercaptopropanol (BAL), and certain other mercaptans are specifically depressor in animals; sodium azide has a similar rather transient effect; 8-hydroxyquinoline and ethylenediamine tetra-acetate are antihypertensive in rats; and certain thiopseudouracilues and thiosemicarbazide have this common property. All appear to act specifically upon hypertension, either experimental, clinical, or both. The discovery by Tipton and her associates of large amounts of presumably abnormal trace metals in American human tissues has led to considerable speculation and to some experimental work. The startling finding of Tipton and her co-workers was the presence of an enormous amount of cadmium in the human kidney, up to 33 mg. per kilogram. Cadmium did not appear in several infants, was there in smaller quantities in an older child, but was present in all adults studied. We do not know how it got there, but its concentration was half that of essential zinc. Truly it appears that trace metals may be involved in hypertension and the best lead we know of lies in their removal from the body by better chelating or binding agents.

A Physician: You have implied that hypertension is no longer a problem in your patients. Is that so?

Dr. Schroeder: Within the limits we have stated, that is true. Our cooperative patients are no longer dying of its secondary effects, congestive heart failure and uremia. What deaths we have are usually the results of atherosclerotic thromboses of coronary or cerebral vessels. Atherosclerosis is now clearly the culprit.

A Physician: What about the newer drugs? We are now and probably shall be in the future invited by advertising claims, both direct and indirect, to believe that this or that agent or combination is the answer to our problem. Would you care to draw any general conclusions as to the general efficacy of drug therapy for hypertension in the future?

Dr. Schroeder: It is proper to do a little theorizing and predicting. Bearing in mind the dual or triple pathogenetic mechanisms operative in severe hypertension, one can safely say that no agent acting solely upon autonomic nerves can ever be more effective than total sympathectomy. Therefore, newer ganglionic blocking agents may be more readily absorbed, act more on sympathetic than on parasympathetic functions, act for longer intervals and more evenly, produce fewer side effects, be more potent on a weight for weight basis and be preferred to the older, time tested drugs. While the effects of their use in milder stages of the disease may be excellent, it is unlikely that they can do better than permanent surgical removal of nerves. Very long acting sympatholytic agents may be developed which will be free of serious side effects, but the same statement holds true. For those acting on the mid-brain, of which many will be discovered, now that the door of specific action has been opened by reserpine and chlorpromazine, no agent can be more effective than the relative influence which the mid-brain bears to the total picture.

It is our belief that reversal and, perhaps, eventual cure can be only accomplished by drugs which will do what hydralazine does basically. Therefore, much time and effort must be spent to understand its fundamental actions. Sympathetic nerve blockade alone will be limited to mild stages, but severe cases need a double-barreled approach. The day when one specific drug will control all cases without careful supervision is far distant.

Concluding Remarks: Modern antihypertensive drugs require intelligent handling by both physician and patient. When so employed, the results are usually gratifying to the patient. As a first approximation of specific treatment, they are the best we have. In spite of our overstressing their toxicities, actually they are much less hazardous than some popular drugs and their use is well-justified by the seriousness of the disease which they can control. Fatalities due to the drugs themselves are rare. Their side effects which vary with their potencies are sometimes distressing but seldom require discontinuation. There are enough drugs now available to control the hypertension and promote longevity of almost any patient who wants to be treated and will submit to therapeutic inconveniences.
The Treatment of Hypertension with Modern Drugs
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