Studies on the Control of Hypertension

VI. Some Evidence for Reversal of the Process During Hexamethonium and Hydralazine Therapy

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

Because doses of antihypertensive agents necessary to control human arterial hypertension at relatively normotensive levels were observed to decrease with time, records of all patients in our series receiving oral hexamethonium chloride and hydralazine (but no other drugs) were analyzed (114 cases). After two years of therapy, those patients maintaining average diastolic pressures below 100 mm. Hg were found to require considerably less methonium ion while those unable or unwilling to control their pressures to this degree needed approximately their initial doses. Further decreases in drug requirements for the well-controlled group occurred after three years. Ten were able to discontinue all medication eventually and nine others needed only smaller doses of hydralazine; in these reversal of secondary changes was sometimes observed. Prolonged, continuous and adequate drug therapy is apparently associated with a change in the basic process producing hypertension.

After the first consistent successes in chronically lowering markedly elevated human diastolic pressure to normal or nearly normal values by autonomic blockade plus oral hydralazine, interest was aroused as to the permanence of the change or lack of it. Although the side effects of therapy gradually dwindled in a manner reminiscent of the tolerance characteristic for methonium compounds, no tolerance to the antihypertensive effect of the combined treatment has been observed after four years. On the contrary, a progressive diminution in drug requirement has frequently been observed. Moreover, after varying periods of induced normotension, some patients, including an occasional one who originally had severe diastolic hypertension, have been gradually able to diminish and eventually to discontinue treatment entirely, without re-elevation of blood pressure. To ascertain the magnitude of such trends, the dosage and blood pressure data for our patients orally treated with hydralazine and hexamethonium chloride have been tabulated. This paper indicates the overall results and discusses in some detail those patients who no longer require autonomic blocking agents. Because generalized vasospasm, and not secondary atherosclerosis, was being affected by the drugs, the severity of the disease encountered is considered mainly in terms of blood pressure.

Method

Every patient with high blood pressure discharged from Barnes Hospital between August of 1951 and May of 1954 after treatment by us with both oral hexamethonium chloride and hydralazine, but no other antihypertensive agent, was included in the study, provided that adequate daily follow-up data were available for at least one year, that there was no evidence of delayed hydralazine toxicity or other intercurrent condition, and that other vasoactive drugs, particularly the Rauwolfia or veratum alkaloids and newer ganglionic blocking agents, were not added to the regimen during the period in question. Unfortunately, a considerable number of the more severely hypertensive patients had to be removed from the series because of replacement of hexamethonium with pentapyrrolidinium ion or the addition of reserpine. Of the 114 individuals who fulfilled the criteria, 59 were white males, 13 were Negro, and 29 were ward patients. The average age was 46 with a range from 24 to 65 years. Although nine had been surgically sympathectomized at the time of first entering the hospital, none was following any effective antihypertensive regimen other than sodium restriction.

The pretreatment control diastolic pressure taken with the patient at rest in bed exceeded 100 mm. Hg.

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in all instances and it was felt that both ganglionic blockade and hydralazine were needed to produce normotension. The pretreatment value for each patient was the mean of all supine readings taken by nurses at four hour intervals day and night in the hospital before any drugs were given. The mean number of measurements averaged for each patient was 18. A minimum of 10 readings were available except in the cases of five individuals admitted as emergencies because of signs of cerebral edema and a diastolic pressure greater than 150 mm. Hg.

Fundoscopic examination, urinalysis and a determination of the level of nonprotein nitrogen in the blood was carried out in all cases. Hemorrhagic and/or exudative retinitis was observed in 39, of whom 10 showed edema of the optic nerve as well. Twenty-eight had 1 to 4 plus albuminuria and 26 more a trace of protein in their urine. Thirteen were azotemic with an average of 41 mg. of nonprotein nitrogen per 100 ml. of plasma. * The mean excretion of intravenously injected phenol red within 15 minutes was 19.9 per cent in the 102 tests for which the urine volume was adequate. In 32 of the 66 instances when a sodium amytal release test was performed, the diastolic pressure remained above 90 mm. Hg, the minimum reading averaging 106 mm.

In the hospital, the average diastolic pressure was controlled with a constant dose of oral hydralazine at four-hour intervals and simultaneously a variable dose of oral hexamethonium chloride depending on the level of the sitting systolic pressure. Each patient obtained a sphygmomanometer and adequate instruction in its use. To each was explained his hospital regimen which he was instructed to continue at home. After discharge, each kept a daily record of his blood pressure and medication, which were collected upon his return. For 33 who required further regulation in the hospital, a check on the validity of the patient’s own records was available; agreement was excellent. Pertinent laboratory data were gathered at suitable intervals by the same laboratory which made the pretreatment observations. No other drugs, dietary regimens, or therapy of any kind was employed.

Because of difficulty in grading the severity of the hypertensive process objectively, the patients were divided into three arbitrary groups solely on the basis of their pretreatment diastolic pressures, no account being taken of the presence or absence of serious secondary manifestations, such as congestive heart failure, cerebrovascular accident, coronary occlusion or renal functional impairment. Forty patients were in the so-called mild group with control diastolic pressures from 100 through 114 mm.; 41 were in the moderate group with pressures from 115 through 129 mm. and 33 were in the severe group with pressures from 130 through 180 mm. Hg. * The average pretreatment systolic pressures at rest for the three groups were 221, 193, and 179 mm. Hg respectively. A posttherapeutic diastolic pressure of 100 mm. Hg was arbitrarily chosen to divide each of the three groups into a so-called controlled and an uncontrolled subgroup. These pressures were calculated for the pair of weeks, exactly one month and one year after hospital discharge; † when they were

* For the sake of simplicity throughout the paper the italicized terms mild, moderate, and severe each designates a group of patients as defined in the text solely by their pretreatment diastolic pressures. This grouping is not to be confused with that previously used. 2 Of the patients here discussed nine had "moderate benign" stages of hypertension by the more usual classification, 66 had "severe benign" stages and 39 had "malignant" or "premalignant" stages, the latter with resting diastolic pressures above 120 mm. Hg and normal optic discs but with hemorrhagic and/or exudative retinitis and gravely impaired renal function. Similarly the italicized terms controlled and uncontrolled designates the subgroups of patients as defined in the text solely by their posttherapeutic diastolic pressure. For simplicity’s sake in comparing values of both blood pressure and dosages, the period beginning one month after hospital discharge will several times be indicated as the initial posttreatment period to distinguish it from the periods beginning 1, 2 or 3 years following discharge.

† The blood pressure and the dosage of medication immediately before hospital discharge is an unfair base of comparison for the follow-up data since the period of control is brief and often does not represent a steady state. Diastolic pressure and drug intake for the last 48 hours in the hospital, for the first week at home and for the pair of seven day periods beginning exactly one and two months after discharge were calculated for a considerable number of patients. The first two were different from each other and from the last two, which, on the other hand, were quite similar. Using a fortnight instead of a week was carefully checked and found to be no more reliable; seldom was the variation between two consecutive weeks more than 10 per cent with respect either to blood pressure or drug intake. On this basis, the seven-day period, exactly one month following discharge from the hospital, was used to obtain the initial posttreatment blood pressure and dosage levels. Since warm weather lowers both the blood pressure and the hexamethonium requirement, only yearly follow-ups obviated seasonal bias and hence were considered worthwhile.

* The maximal normal level of nonprotein nitrogen in the blood after deproteinization by zinc hydroxide as used here (Somogyi, M.: Method for preparation of blood filtrates for determination of sugar. J. Biol. Chem. 86: 655, 1930) is 26 mg. per 100 ml. The low value is due to removal of glutathione, ergothioneine, uric acid and perhaps other substances which are not precipitated by the more usual phosphotungstic acid procedure.
available similar two-year and three-year follow-up analyses were obtained. The individual values for each patient were gotten by averaging either 35 or 28 recorded blood pressure readings and dosages of each drug, depending on whether the patient took his medicine four or five times a day. Each of the figures for a group or subgroup cited in the text or in a table is the mean of the individual values for all the patients involved. Over 20,000 separate measurements of blood pressure were analyzed. Because of the variation in initial dosage from patient to patient, the percentage change was determined at annual intervals. Hence the follow-up hexamethonium and hydralazine intakes are expressed as ratios, being the daily grams ingested 1, 2, and 3 years after discharge from the hospital, divided by the daily grams ingested one month after discharge. Patients were not included in the figures anytime subsequent to discontinuation of one or both drugs, unless permanent normotension had been achieved.

**RESULTS**

After a month of treatment the average daily intake of oral hexamethonium chloride was 2.11 with extremes of 4.80 and 0.63 Gm. The dose was less than 1 Gm. per day in only six cases of which two were azotemic and one a sympathectomized patient. The comparable mean dose of oral hydralazine was 0.52 with extremes of 1.24 and 0.13 Gm. per day.

Table 1 indicates that the lower the pretreatment diastolic pressure the greater the likelihood of prolonged post-treatment control. Even in the severe group, however, the majority had diastolic pressures less than 100 mm. Hg after a year of therapy. In all three of the controlled subgroups a similar or lower diastolic pressure was maintained by less autonomic blocking agent after a year than initially,* but only an equivocal decrease in hydralazine ingestion occurred. The diminution in use of both drugs was greatest for the mild group. In contrast, there was no change in dosage or diastolic pressure for any of the three uncontrolled subgroups.†

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* The diminution and eventual discontinuation of hexamethonium chloride is an automatic process dependent only on the patient's dosage schedule whereby the full dose is taken for a sitting systolic pressure over 140 mm. Hg; half of a dose for a pressure between 130 and 140 mm. and a fourth of a dose for a pressure between 120 and 130 mm. There is no comparable automatic decrease in the dose of hydralazine since the regimen calls for a constant intake until it is reduced by the physician.

† Most individuals in the uncontrolled subgroups either refused to increase their doses or were not urged to do so because of the presence of azotemia, old cerebral vascular accident or other secondary atherosclerotic complications. A few were deliberately maintained on their initial doses in order to observe whether or not their moderate or mild hypertension diminished. Sufficient doses have usually resulted in control.
Choosing the data in another manner and considering only the controlled subgroups, 7 of 19 in the severe group, 9 of 27 in the moderate group and 13 of 32 in the mild group required less than half the initial post-treatment dose of methonium after a year. Two, 3 and 6 patients respectively needed less than a fourth of their blocking agent; and 1, 1, and 5 less than an eighth.

The first part of table 2 gives comparable results after two years of therapy for the 78 patients on whom adequate records are available. A downward trend of diastolic pressure in all three controlled subgroups is obvious. There is a further decrease in the hexamethonium requirement which is particularly evident for controlled patients of the mild group, 28 of whom required an average of only 37 per cent of their initial dose of blocking agent. There is a similar, but less marked decrease in the dosage of hydralazine.

The second part of table 2 lists the values for the 38 patients whose records are available for three years. The small numbers reduce the significance, but the previously mentioned two-year trends can be seen. It appears that the uncontrolled subgroups, unlike their controlled counterparts, had no definite change in diastolic pressure or dosage of drugs after two and three years.*

* Ten patients in the moderate and severe groups were dropped from the series after completing one or two years of therapy because pentolinium tartrate was then substituted for hexamethonium chloride. Three had been controlled but side effects were bothersome. For them the same degree of control continued with little amelioration of symptoms after the substitution. Their mean diastolic pressure on a daily average of 1.52 Gm. of hexamethonium chloride had been 88 mm. Hg and on 0.39 Gm. pentolinium tartrate was 91 mm. Hg. In 7 of the 28 patients in these two groups who had not been controlled at the end of one year, primarily because of excessive side effects, the change in regimen was made in an effort
and at two years it was 0.06 Gm. of pentolinium tartrate which is approximately equivalent to 0.30 Gm. hexamethonium chloride. At three years it was 0.03 Gm. of pentolinium tartrate. The intake of hydralazine was 0.75, 0.15 and 0.025 Gm. at one, two and three years, respectively. The blood pressure has consistently remained below 140/90 mm. Hg and the 15 minute phenol red excretion has increased to 17 per cent.

Table 3 gives the individual data for those who were able gradually to decrease their doses of autonomic blocking agent and finally discontinue it while still maintaining an essentially normal diastolic pressure. Of the 19 patients, 10 had discontinued their hydralazine as well at the month indicated. All in the severe group had originally had electrocardiographic abnormalities, most had had albuminuria and half had had hemorrhagic retinitis. Considerable electrocardiographic evidence of disease, but few of the other changes beyond elevated diastolic pressure, had been present in the other two groups.

Eight patients of the 114 in the series died after an average of 26 months from the beginning of therapy. Three were not controlled, one year after starting treatment, because of intermittent discontinuation or insufficient dosage. In the other five the diastolic pressure had remained below 100 mm. Hg for a year; however, in 2 at least and probably in 2 others, therapy was lessened to the point of a re-elevation of blood pressure before death. A cerebrovascular accident was the terminal event in six. One died of cardiac rupture after myocardial infarction. The other, who had had a pretreatment diastolic pressure of 176 mm. Hg; hemorrhagic and exudative retinitis with edema of the optic nerves, and azotemia, died of renal failure after 30 months of treatment.*

The problem of patients passing from a controlled to an uncontrolled subgroup was never encountered in analyzing a patient's

* This patient was in fairly good health with well-controlled blood pressure in spite of slowly progressive azotemia (pretreatment nonprotein nitrogen of 61 mg. per 100 ml. of blood rising in 30 months to 103 mg.). Terminally, a severe gastrointestinal hemorrhage precipitated shock and uremia. Both kidneys together weighed only 105 Gm.
Table 3.—Initial Intake and Length of Therapy in 19 Patients who Discontinued Methonium with a Comparison of Pre- and Post-Treatment Laboratory Data

<table>
<thead>
<tr>
<th>Meth. at 1 Mo.</th>
<th>Time Meth. Discont.</th>
<th>Fraction of Initial Hydral.</th>
<th>Diastolic Pressure</th>
<th>Optic Fundi</th>
<th>Albuminuria</th>
<th>% PSP in 15 Minutes</th>
<th>ECG</th>
<th>Index of Improvement</th>
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<td>Gm./day</td>
<td>Months</td>
<td>mm. Hg mm. Hg</td>
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<td>92</td>
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Table 3 gives detailed data on 19 patients who without compromising their normotension have been able in periods from 12 to 39 months to diminish gradually and eventually discontinue the blocking agent (hexamethonium chloride, Ca) which was found necessary to control their hypertension. Four had pretreatment diastolic pressures of 130 mm. Hg or higher; 6 had pressures from 115 to 129 and 9 had pressures below 115. The next to the last patient in the table had been sympathectomized prior to drug therapy, which may explain the low initial dosage of hexamethonium chloride and the relatively high diastolic pressure at 30 months. Ten of these patients have been able to discontinue completely their hydralazine.

The first column indicates the average daily dose of hexamethonium after a month at home in the manner of table 1 and the text. The second column lists the number of months at which methonium medication was automatically terminated and the third indicates the dose of hydralazine at that time. The next five pairs of columns tabulate the control values and the values at the end of discontinuation of methonium for five laboratory evidences of the severity of hypertension. The pretreatment diastolic pressure is the previously discussed mean. The sixth and seventh columns show when hemorrhages (h) and/or exudates (e) were present in the optic fundi; the next pair, the presence or absence of albuminuria; the next pair, the 15-minute excretion of intravenously injected phenol red when the urine volume was at least 50 ce; and the final pair, electrocardiographic interpretation.

Abbreviations: ischem. = myocardial ischemia, LVE = left ventricular enlargement, normal = within normal limits and damage = myocardial damage. A final column has been added to summarize the changes in the fundi, urine, renal function and electrocardiogram. Any improvement between pretreatment and posttreatment values in these columns was counted as one. Many of the changes in any individual are not significant; however, the generalized nature of the improvement may be. The means for several of the columns are given underneath each of the three groups and, in several instances, are expressed as the number with an abnormality over the total number in the group.
records. Instances cited in the previous paragraph were discovered only after the terminal episode. Eight patients moved in the reverse direction from an uncontrolled to a controlled subgroup between the first and second years of therapy. Eighteen other patients who were uncontrolled after one year, and for whom a two-year follow-up is available, did not change their status over this interval. Patients who keep adequate records for one year generally continue to do so. Of the 86 who began therapy more than 24 months ago, 78 have adequate two-year follow-up records while only eight have not communicated with us for three months.

There are an additional eight, currently normotensive, patients who have discontinued methonium medication, four of whom have discontinued hydralazine as well. They have not been included in the series because of the addition of Rauwolfia alkaloids to their regimens. All but one would have been in the mild controlled subgroup.

**Discussion**

This paper concerns itself with the relationship between blood pressure and drug dosage and how it changes with time. To avoid confusion only one antihypertensive regimen is considered. Laboratory and clinical data are treated more fully elsewhere. They are mentioned here only to demonstrate the severity of the hypertension.

The 114 patients were all considered to have serious hypertension. Their mean diastolic pressure at hospital rest was 123 mm. Hg. Almost half of the sodium amytab release tests did not result in diastolic normotension, and about half of the urinalyses revealed protein. Severe renal damage and hemorrhagic retinitis were common. In each case autonomic blockade plus hydralazine were either found or deemed necessary to achieve and maintain normal blood pressure. The data of tables 1 and 2 substantiate the longstanding clinical impression that a diminishing requirement for both blocking agent and hydralazine in order to maintain normotension occurs with time. This lessened need for drugs suggests that the hypertension slowly alters to a stage less severe than at first. Increased sensitivity to the drugs, however, is not apparent in patients whose diastolic pressure remains distinctly elevated, even though it may have been lowered somewhat by therapy. Moreover, real tolerance follows discontinuation of the drug as in the previously reported case where the initial normotension effected by 1 Gm. of oral hexamethonium chloride daily could not be matched by less than 2.5 Gm. of oral pentolinium tartrate after treatment was once stopped and could not be approached by 4 Gm. of intramuscular pentolinium tartrate after the second discontinuation of autonomic blocking agent.

There was no obvious pretreatment difference between those patients who were controlled by drugs and those patients who remained uncontrolled, yet after a year of therapy, 79 of the former needed an average of only 73 per cent of their initial blocking agent while 35 of the latter were still taking 97 per cent of it. At the end of two years, the percentages of blocking agent ingested by the two groups of patients were 57 and 99 respectively. Less definite were the comparable figures for hydralazine intake which were 89 and 93 per cent at one year and 71 and 86 per cent at two years.

Ten of 114 patients, including a pair in the severe group, were gradually able to discontinue all treatment without compromising their new-found normotension. Other laboratory evidence (table 3) for pretreatment cardiovascular and renal involvement substantiates the diastolic pressure as a measure of significant hypertension. Moreover, the trend toward normalcy noted in the objective tests following prolonged normotension suggests that lowering the blood pressure is worthwhile, since it allows some secondary manifestations of the pathologic process to reverse. Evidence of such regression has previously been observed for those severely hypertensive individuals who have the greatest opportunity to show this effect since they have the maximum pretreatment deviation from normal.
It must be reemphasized that automatic and gradual withdrawal of drug therapy which accompanies prolonged normotension is very different in its overall result from sudden early discontinuation because of inconvenience or unpleasant side effects. The former results in apparent, although perhaps temporary, "cure" while the latter is usually fatal in sufficiently severe cases or leads to a recrudescence of the original hypertension in milder ones.

The extent and direction of the systematic bias of the results is unknown. There is a tendency to lose both the best and the worst results to follow-up. The latter drop out to seek help elsewhere and the former are "cured" and need no help. Division into controlled and uncontrolled subgroups with 100 mm. Hg as the dividing line can be criticized. Depression of the diastolic pressure from 101 to 99 mm. Hg is hardly significant, whereas a depression from 150 to 101 may well be life-saving. In order to be fully objective, however, it was felt necessary to be somewhat arbitrary.

**Summary**

One hundred and fourteen patients with hypertension of varying degrees of severity were followed closely during at least one year of carefully controlled therapy with an oral combination of hexamethonium chloride and hydralazine without other drugs. At the end of this period, 79 patients who had maintained diastolic pressures below 100 mm. Hg required only 73 per cent of their initial dose of blocking agent; whereas 35 whose hypertension had not been so reduced were still taking 97 per cent of their initial dosage. The 78 patients who were similarly followed for two years and the 37 who were followed for three years reinforced the suggestion that, following normotension or near normotension, the dosage of antihypertensive drugs diminished with time, whereas with less adequate control of blood pressure the required dosage remained unchanged. In 19 normotensive patients, this trend had extended to the point of complete discontinuation of hexamethonium chloride and in 10, to the discontinuation of hydralazine as well, without a recrudescence of hypertension.

**Acknowledgment**

We are indebted to Betty F. Perry for the extensive mathematic calculations.

**SUMMARIO IN INTERLINGUA**

Cento dece-quatro patientes con hypertension de varie grados de severitate esseva observate durante un anno o plus de un cautemente contolata therapia oral a chlorido de hexamethonium combinata con hydralazina. Nulle altere droga esseva usate. Al fin del periodo, 79 patientes qui habeva mantenite pressiones diastolic infra 100 mm Hg requireva solmente 73 pro cento de lor dose initial del agente blocator, durante que 35 patientes qui non habeva attingite un simile reduction de lor hypertension prendeva ancora 97 pro cento de lor dose initial. Septanta-octo patientes esseva similemente observate durante duoannis e 37 patientes durante tres annos. Le observationes de lor casos reinforciava le notion que post le attingimento de normo- o quasi-normotension, le requisite doses del drogas antihypertensive se reduce in le curso del tempore, durante que in casos de minus adequate domination del pression sanguinee, le requirimento de dosage remane incambiate. In le caso de 19 patientes normotensive, iste tendentia attingeva le puncto del complete discontinuation de chlorido de hexamethonium. In 10 de ille casos etiam le hydralazina esseva discontinuate. Nulle de iste patientes experienciava un recrudescentia del hypertension.

**REFERENCES**

4 Perry, H. M., Jr., Schroeder, H. A. and Mor-
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