Studies on the Control of Hypertension by Hyphex

I. Effects on Blood Pressure

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This report is the first of a series on a method for treatment of hypertension by oral hexamethonium chloride and hydrazinophthalazine. When strictly followed blood pressure was maintained at reasonable or normal levels in 80 per cent of 258 cases of severe hypertension. The malignant stage, when present, was reversed. Renal insufficiency and severe cerebral atherosclerosis limit the effectiveness of the method for prolongation of life.

A METHOD effective for sustained control of the elevated arterial pressure of chronic hypertensive disease has been developed and employed in over 250 patients since August 1951. The purposes of the investigation were (1) to ascertain whether or not treated hypertension was compatible with a return to health in patients suffering from its effects; (2) to determine whether or not the method was "specific" in the sense that pathogenetic and secondary influences were favorably altered; (3) to define the limits of the method in terms of severity of disease and alterations toward normal; (4) to detect late "toxic" effects or new diseases caused by the agents employed; and (5) to discover what hazards, if any, accompanied alterations of long standing cardiovascular abnormalities.

Because the use of any method for treatment of hypertension is controversial, and because the present one has shown conclusively that sustained control can be achieved, we are reporting our experiences in detail. This report deals only with alterations of elevated arterial blood pressure in a series of cases selected for representing as severe forms of arterial hypertension and its complications as have been encountered in a general hospital. The accompanying communication deals with fatal and serious conditions caused by the agents employed. Others will discuss special problems, such as congestive heart failure, angina pectoris, malignant hypertension, renal insufficiency and the effects of poor management.

Method

The method is based on the assumption that at least two influences act concurrently to cause generalized vasoconstriction and hypertension; therefore both must be counteracted simultaneously if elevated arterial pressure is to be controlled. One influence is presumably neurogenic, acting through the medium of the autonomic sympathetic nerves. The ideal drug for counteracting this influence is a true sympatholytic agent; unfortunately none so far has been encountered which could be tolerated for months and years of continuous use. Therefore ganglionic blockade by quaternary ammonium salts was utilized. Hexamethonium chloride serves the purpose well,
can be taken orally with safety under certain precautions, and is nontoxic in the sense that "side effects" are the result of its primary action. Sympathetic nervous inhibition is achieved, however, at the expense of parasympathetic nervous inhibition, which can at times be distressing. The drug is excreted rapidly in the urine and therefore must be taken at frequent intervals. No case of severe hypertension encountered has been controlled adequately by this agent alone.

The second influence is presumably nephrogenic and concerns bloodborne vasoconstrictor substances. Of these, pherentasin is one positively identified in hypertensive arterial blood. 1-Hydrizinophthalazine is a true antihypertensive agent of moderate potency; it acts as a carbonyl reagent, binds heavy metals and sulfhydryl compounds and possibly combines directly with the carbonyl group of pherentasin. In large doses it has the property of abolishing the vasopressor actions of certain, but not of all, primary amines. It can be taken orally for indefinite periods of time. When first given, it can exhibit "side effects" due probably to its primary action on other systems than those concerned in hypertension; when the action of the autonomic nerves is inhibited, side effects are lessened. It is excreted fairly rapidly and therefore must be taken at regular intervals. Few cases of severe hypertension encountered have been controlled adequately by this agent alone.

The method is as follows:

The patient must be in hospital. Blood pressure is measured in the supine position every four hours, day and night. Renal function is estimated by the 15, 30 and 60 minute excretion of intravenously injected phenol red (P.S.P.) and the nonprotein nitrogen level of the blood, renal pathology by intravenous pyelography and the state of the urea, cardiac pathology by electrocardiography and x-ray, the state of the blood vessels by funduscopic examination. Hexamethonium chloride is given by mouth and increased to effective levels at a rate depending upon one's estimate of the severity of the hypertension, its lability, and the amount of vascular damage, especially cerebral. Every effort is made to "undershoot" the dose, and to build up toward the desired effect. Dosage schedule is changed daily, slowly, and carefully, depending upon the record of the previous day. 1-Hydrizinophthalazine is added later. A typical schedule for a case of severe arterial hypertension without renal insufficiency or marked cerebral atherosclerosis follows:

1st day—125 mg. hexamethonium chloride every four hours. Omit dose if systolic pressure is below 140 mm. Hg.

2nd day—250 mg. hexamethonium chloride every four hours

3rd day—375 mg. hexamethonium chloride every four hours

4th day—500 mg. hexamethonium chloride every four hours. Omit part or all of dose, depending upon level of systolic pressure, as described below.

5th day—Same plus 25 mg. 1-hydrizinophthalazine every four hours

6th day—Same plus 50 mg. 1-hydrizinophthalazine every four hours

7th day—Same plus 75 mg. 1-hydrizinophthalazine every four hours

8th day—Same plus 100 mg. 1-hydrizinophthalazine every four hours

The establishment of normotension would interrupt and stabilize the above schedule at any point.

Routine orders are as follows: (1) Measure blood pressure before each dose (every four hours) and record on graphic chart. (2) Give --- mg. (full dose) of hexamethonium chloride if systolic pressure is 140 mm. Hg or above. (3) Give --- mg. (1/2 dose) of hexamethonium chloride if systolic pressure is between 130 and 140 mm. Hg. (4) Give --- mg. (1/4 dose) of hexamethonium chloride if systolic pressure is between 120 and 130 mm. Hg. (5) Omit all hexamethonium chloride if systolic pressure is below 120 mm. Hg. (6) Do not omit 1-hydrizinophthalazine. (7) Give cascara and milk of magnesia or other mild laxatives every evening if no bowel movement that day. Do not allow patient to become constipated. Do not use "bulky" laxatives or "roughage." Use irritative and saline laxatives. Citrate of magnesia is given in the morning if the evening laxative is not effective. It is essential that the patient have a bowel movement every day. (8) Use urecholine for distention, severe constipation and retention of urine in the bladder. (5-10 mg. by mouth. Do not give parenterally as severe reactions may occur; the parasympathetic nervous system is probably sensitized to peripherally acting cholinergic drugs.)

In the most severe cases, the dose of hexamethonium chloride may be increased to 1.0 Gm. every four hours and of 1-hydrizinophthalazine to 200 mg. every four hours; 750 mg. and 150 mg., respectively, per dose will be adequate to control over 90 per cent of cases. At these levels severe constipation may be intolerable unless bowels are kept open daily.

A few days prior to discharge from hospital, the doses given at 2 or 4 a.m. are omitted; generally this results in a slight rise in the blood pressure taken at 6 or 8 a.m. The patient or a member of the family is instructed in the use of the sphygmomanometer,
and measures his own blood pressure before each dose, checking the readings frequently with an experienced observer. At home, he follows the same regimen, with drugs at four hourly intervals, except for one interval at night; the dose of hexamethonium chloride is omitted or reduced according to the prevailing level of systolic pressure. If blood pressure cannot be conveniently measured (as at work), the patient may estimate hypotension by standing quietly for a minute in order to induce faintness. It is essential that the full dose of hexamethonium chloride not be taken when the systolic pressure is normal; hypotension will follow within two hours and distressing reactions may result. The analogy of the control of diabetes with insulin and the control of hypertension with Hyphex is obvious.

**Material**

All patients were accepted for treatment because hypertension had been severe, persistent, and had failed to respond to the usual methods or had caused secondary damage to heart, brain, or kidneys. The presence of persistent chronic hypertension had been well documented in every case. For example, 25 suffered from congestive cardiac failure; 43 exhibited various degrees of renal insufficiency with retention of nitrogen in their blood; 35 had suffered one or more cerebral vascular accidents, 35 a coronary occlusion; 12 exhibited signs of deterioration consistent with cerebral atherosclerosis and 8 were severely ill with acute cerebral edema. Their ages ranged from 6 to 80 years; the majority were in the fifth and sixth decades of life, although those exhibiting the malignant stage (89 cases) tended to be younger. Most patients were referred either by other physicians, or in some instances, by patients themselves under treatment; a few had been followed for several years in the outpatient department. No individual whose blood pressure fell with rest in bed and sedation to sustained systolic levels below 180 mm. Hg and diastolic levels below 120 mm. was accepted for treatment. Of the first 100 patients, all showed signs of severe disease and were handicapped by it to various degrees; of the second 150, the requirements for treatment were broadened to include some individuals exhibiting only electrocardiographic evidence of cardiac abnormalities, roentgenographic signs of cardiac enlargement, slight diminution of renal function or severe headaches without definite secondary pathology. It was believed at the beginning of the study that the most vigorous test of the method should be made in advanced cases in order to define the limits of effectiveness. All of our experience, which of necessity includes serious reactions occurring during pioneering attempts now avoided, will be reported in this series of papers.

**Method of Analysis**

Blood pressure was measured every four hours in hospital by competent nurses and charted. At home, blood pressure was measured by the patient or a member of his family five times a day and charted. Since the levels measured by physicians may be considerably higher than those obtained by nurses and technicians in certain individuals, a comparison was made between "nurses' levels" and "patients' levels" rather than between those obtained by physicians and patients, which would have made the alterations appear greater. "Resting" levels were included in those measured at 2 a.m. and 6 a.m.

The initial stage of the hypertensive disease present in each individual was estimated according to standards which we have found useful. Since some of the secondary effects of hypertension, such as coronary arterial occlusion and cerebral accident, are not directly caused by hypertension but rather are the result of atherosclerosis, and since treatment is aimed at control of blood pressure at as normotensive levels as feasible, atherosclerotic complications were not considered in evaluation of the stage of hypertensive disease. The various stages pertinent to this study are as follows*:

**II. Moderate Benign Hypertension.** Blood pressure always elevated at rest in bed but falls to normal levels during heavy sedation with Sodium Amytal. Ocular fundi, grade I or II (Keith-Wagener). Renal function as measured by the 15 minute excretion of phenol red (P.S.P.) normal or nearly normal (25 per cent or greater). Diastolic pressure usually 105 to 120 mm. Hg, systolic 180 to 220 mm. during rest in bed.

**III. Severe Benign Hypertension.** Blood pressure not falling to normal during sleep induced by Sodium Amytal. Ocular fundi, grade I or II. Renal function normal or depressed without retention of nitrogen in blood. Diastolic pressure usually 120 to 160 mm. Hg; systolic 200 to 270 mm. during rest in bed.

**IVa. Early Malignant Hypertension.** Diastolic pressure always 130 to 160 mm.; systolic 200 to 280 mm. Renal function reduced but without retention of nitrogen in blood. Ocular fundi, grade III. Albuminuria and abnormal microscopic elements present.

**IVb. Severe Malignant Hypertension.** Diastolic pressure always 130 to 200 mm. Hg; systolic 200 to 300 mm. Borderline renal func-

* Stage I represents mild benign hypertension, the blood pressure being at normal levels during complete rest, the systolic varying from 150 to 180 mm. Hg and the diastolic 90 to 105 mm. during activity. Stage 0 represents prehypertension, the blood pressure being at normal levels (below 140 and 90 mm.) except under stress.
tion or slight elevation of nonprotein nitrogen in blood (up to 30 mg. per cent; upper limit of normal by method 25 mg.). Ocular fundi, grade IV.

In order to assess the results of treatment, we have set up arbitrarily certain rather rigid therapeutic grades, into which each patient was placed according to the findings during the latest month of therapy at the time of writing. These grades were chosen in order to provide an index of the prevailing level of blood pressure; the task of calculating average levels for each patient based on five readings a day for even one month's time is enormous and unrewarding, as fluctuations usually occur daily. We consider the grading of prevailing levels more indicative of the results of therapy than a consideration of the average reduction of pressure. Only in the case of patients show-

### Table 1.—Effects of Hyphex on Blood Pressure, All Cases, 6 to 25 Months

<table>
<thead>
<tr>
<th>Therapeutic Grade</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 3 2 1 0</td>
<td>4 3 2 1 0</td>
<td></td>
</tr>
<tr>
<td><strong>Initial Stage of Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Living</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVe</td>
<td>5 5</td>
<td>3 6 1 1</td>
<td>21</td>
</tr>
<tr>
<td>IVb</td>
<td>4 3 1</td>
<td>4 2 2</td>
<td>16</td>
</tr>
<tr>
<td>IVa</td>
<td>1 4 2</td>
<td>4 7 2</td>
<td>20</td>
</tr>
<tr>
<td>III</td>
<td>11 29 11 1</td>
<td>15 39 16 2</td>
<td>124</td>
</tr>
<tr>
<td>II</td>
<td>4 3 1</td>
<td>9 1 3</td>
<td>21</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0 17 46 19 3</td>
<td>25 63 22 6</td>
<td>202</td>
</tr>
<tr>
<td>White Dead</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVc</td>
<td>2 3 1</td>
<td>1 2 3</td>
<td>2</td>
</tr>
<tr>
<td>IVb</td>
<td>2 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVa</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0 3 6 3 0</td>
<td>3 2 3 2</td>
<td>2 24</td>
</tr>
<tr>
<td>Negro Living</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVe</td>
<td>1</td>
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<tr>
<td>IVb</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>IVa</td>
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<td></td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>1 1</td>
<td>3</td>
<td>2 1</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0 1 3 1 0</td>
<td>0 3 3 2</td>
<td>2 15</td>
</tr>
<tr>
<td>Negro Dead</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IVe</td>
<td>2</td>
<td>1 2 2</td>
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</tr>
<tr>
<td>IVb</td>
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<td></td>
</tr>
<tr>
<td>IVa</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
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<td>0 1 4 4 0</td>
<td>0 12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0 24 55 23 3</td>
<td>4 35 73 26</td>
<td>10 253*</td>
</tr>
</tbody>
</table>

* Plus 5 cases of terminal uremia not included in this table.

Grade 3 was deliberately chosen in 18 cases to avoid hypotensive episodes.

IVc. *Decompensated Malignant Hypertension.* Nitrogen retention present. Systolic pressure 200 to 300 mm. Hg; diastolic 130 to 220 mm. unless congestive heart failure is present. Ocular fundi, grade IV.

Certain patients with primary renal disease and renal insufficiency did not fit into these categories; the degree and severity of the hypertension was then estimated, neglecting the renal findings.
ing partial resistance will the latter method be used.

The various therapeutic grades are as follows:

0. Blood pressure always normal, systolic 140 mm. Hg or below, diastolic 90 or below.

1. Normal level of blood pressure 80 per cent of time; systolic never over 160 mm.,
   diastolic never over 100 mm.

2. Reasonable levels of blood pressure. Systolic 160 mm. or below 80 per cent of time,
   never over 180 mm.; diastolic 95 mm. or below 80 per cent of time, never over 110 mm.

TABLE 2.—Lowering of Average Diastolic Pressure in Patients Considered Partly “Resistant” to Hyphex (Therapeutic Grades 3 and 4)*

<table>
<thead>
<tr>
<th>Diastolic pressure continuously reduced by:</th>
<th>Adequately Treated</th>
<th>Inadequately Treated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Living</td>
<td>Dead</td>
<td>Living</td>
</tr>
<tr>
<td>10-20 mm. Hg</td>
<td>4</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>21-30 mm.</td>
<td>13</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>31-40 mm.</td>
<td>9</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>41-60 mm.</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>&gt;60 mm.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>7</td>
<td>117</td>
</tr>
</tbody>
</table>

* Excluding five patients upon whom lumbar sympathetic nerve was performed 3 to 6 years previously and in whom severe hypertension recurred.
† Inadequate for one of the following reasons: Poor cooperation, intermittent cooperation, the presence of renal insufficiency, cerebral vascular disease or severe generalized atherosclerosis for which treatment was given cautiously.

3. Moderately hypertensive levels of blood pressure. Systolic 180 or below 80 per cent of
time, never over 200 mm.; diastolic 100 or below 80 per cent of time, never over 120 mm.

4. Consistently hypertensive levels of blood pressure. Systolic 200 mm. or below 80 per
cent of time, never over 220; diastolic 120 or below 80 per cent of time, never over 130.

The therapeutic responses of all cases could be included in these groups.

RESULTS

In all cases adequately treated blood pressure was considerably lower. When the
diastolic pressure had been elevated to levels of 140 to 160 or more, the systolic pressure was
usually reduced to levels below that point and so maintained. Mishandling of cases by
modification of the method and by omission of the drugs for variable periods of time gave
rise to uniformly poor results.

In table 1 are the gross effects on blood pressure in all cases, both continuing and discontinuing
therapy. The initial stages of the disease and the therapeutic levels of blood pressure sustained are shown. The malignant stage
reversed itself in all cases adequately treated. No striking difference in responses of men and
women was noticed. On the whole, Negro patients did badly. Of 77 white patients in
malignant stages, 78 per cent attained good control of blood pressure and 42 have returned
to full-time activity. Eighty per cent of 85 living white males were able to maintain their
blood pressures at levels considered reasonable or lower (grades 2, 1, 0); 79 per cent of 117
white females were in similar categories. Therefore, in 80 per cent of all cases the blood pressure was controlled at levels of 160 mm. systolic or below most of the time and never exceeded 180 mm. The addition to these statistics of patients dying of various causes alters the results but little. The effects, however, were
not as consistent in patients who were uncooperative or irregularly cooperative.

The reduction of blood pressure in the 20 per cent of cases partly resistant to the drugs is shown in table 2. But for four, the average change of diastolic pressure was greater than 20 mm. Hg. When readmitted to the hospital, all became normotensive at rest. Only one of these four had been in malignant stages; the rest were males with moderate or severe benign hypertension and atherosclerosis.

In a total of 18 patients exhibiting serious secondary complications, such as atherosclerotic cerebral vascular disease or renal insufficiency, the blood pressure was deliberately maintained at high (grade 3) levels; in five of 20 previously subjected to lumbar sympathetic nerve was performed 3 to 6 years previously and in whom severe hypertension recurred.

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the three months between February and May 1953, 14 classified as grade 3 have changed to
grade 2 or better, while none in grade 2 or 1
has changed to grade 3. In 10 patients treated
with 1-hydrizinophthalazine alone for various
reasons, all but four with mild or moderate
hypertension have been classified as achieving
therapeutic responses of only grade 3 or 4.
Likewise three in stage II given hexamethonium
chloride only have been able to control their
blood pressure at grade 3 levels.

The causes of death in both treated and dis-
continued cases is shown in table 3. In 9 of 43,
renal insufficiency present before treatment
progressed to uremia and death; five were in
terminal stages of uremia. Therefore, the sur-
vival rate was relatively low in this group.
Twenty-two have continued treatment and
survived, four discontinued it and died, while

| Table 3.—Cause of Death in Patients Both Receiving Hyphex and in Whom It Was Discontinued |
|-----------------------------------------|----------------------------------|----------------------------------|
| Cause of Death (Hypertensive Complications) | On Hyphex (223 Cases) | Hyphex Discontinued (35 Cases)* |
|                                         | During Initial Hospital Admission | Later | Total | During Initial Hospital Admission | Later | Total |
|                                         | White Negro | White Negro | Total | White Negro | White Negro | Total |
| Congestive Heart Failure                 | 0            | 1            | 1     | 1            | 1            | 1     |
| Coronary Occlusion                       | 1            | 1            | 1     | 1            | 1            | 1     |
| Cerebral Vascular Accident               | 2            | 2            | 3     | 1            | 4            |       |
| Cerebral Edema                           | 0            | 1            | 1     | 1            | 1            | 1     |
| Renal Insufficiency, Developing          | 5            | 3†           | 8     | 3            | 4            |       |
| Renal Insufficiency, Previously present and moderate or marked | 5          | 6            | 12    | 1            | 5            | 8     |
| Subtotal, Hypertensive                   | 5            | 6            | 12    | 1            | 5            | 8     |
| Interstitial Pneumonia                   | 1            | 4            | 5     |              |              |       |
| Pneumonia                                | 1            | 1            | 1     |              |              |       |
| Postoperative Shock                      | 3            | 3            | 6     |              |              |       |
| Unknown but Normotensive                 | 3            | 3            | 6     |              |              |       |
| Subtotal, Other                          | 5            | 5            | 10    |              |              |       |
| Total                                    | 5            | 11           | 6     | 22           | 1            | 5     |

| Summary: Patients in Malignant (IV) Stages | 10 | 13 |
| Died of Acute Hypertensive Complications  | 3  | 10 |
| Died of Progressive Renal Insufficiency   | 9  | 5  |
| Died of Interstitial Pneumonia             | 5  |     |
| Died of Other and Unknown Conditions       | 5  |     |
| Living                                     | 201|     |
| Gross Mortality, per cent                  | 9.9| 43.0|
| Excluding Previous Renal Insufficiency     | 6.1| 35.6|
| White Only, Excluding Previous Renal Insufficiency | 4.2| 27.6|

* Discontinued for the following reasons: Lack of patient cooperation, 19; discontinued by physician, 11; drug fever, 2; became normotensive without drugs, 3.
† Eleven died soon after Hyphex was discontinued.
‡ Two patients died shortly after hexamethonium was discontinued.
renal insufficiency, only three patients died of the usual complications of hypertension while on treatment, and in no case did renal insufficiency develop. On the other hand, cessation of therapy in patients with malignant hypertension was invariably followed by death of hypertensive complications within 2 to 20 days (11 cases). Of the 10 dying of nonhypertensive causes, the lungs of five (four Negro and one white) exhibited interstitial pneumonia at autopsy. The gross mortality in treated patients was 9.9 per cent; of those treated for a while only, 43 per cent. Analysis of the deaths among treated patients revealed that the malignant stage was present in all but two, both of whom exhibited severe atherosclerosis; among those in whom treatment was stopped, four were in benign stages. Therefore, it appears that moderately severe renal insufficiency is a limiting factor in the effectiveness of the method in many, but not in all cases, and that the prognosis in the malignant stage, while very much better than when untreated, is still poor for Negroes and for about one-fourth of white individuals. Excluding renal insufficiency, however, it is fairly good, only one-seventh dying of various other diseases.

**Discussion**

It is obvious that the use of both of these drugs together results in sustained lowering of the elevated blood pressure of hypertensive individuals. No case adequately managed has failed to respond. Once the response has occurred, it is maintained, unless dosage is reduced or omitted. Experience has shown a consistent relationship between level of dosage and response. Tolerance has not occurred when the regimen was strictly followed by the patient; in fact, it has been possible in many cases to reduce the dose substantially after a year or more.

Strict adherence to the regimen is, however, essential for successful control. Modifications of the schedule have caused failures. It is necessary that a constant blood level of both hexamethonium and 1-hydrazinophthalazine be present for blood pressure to be controlled and that "escape" resulting from discontinuation be prevented. By constant attention to bowels and by eliminating or reducing the dose of hexamethonium chloride according to the prevailing level of blood pressure, accumulation of excessive amounts and reactions thereto have been avoided; the oral form of the drug has been safely used for long periods of time by observing these precautions.

Substitution of placebos for one of the drugs was invariably followed by a progressive rise in blood pressure. When treatment had been continued for a few weeks, the rise usually occurred within 12 hours; after a year or more the rise sometimes appeared only after several days. Since the patient was aware of the change, controlled studies of this nature were difficult to make for more than a few days. Patients in malignant stages sometimes died within two to four days after discontinuing Hyphex; therefore administration of placebos was considered too hazardous to attempt. Two patients with renal insufficiency had shown no signs of progression for 8 and 10 months; discontinuation of hexamethonium chloride was followed within a month by death from uremia.

Signs of the malignant stage of hypertension disappeared completely in the 63 patients surviving, with none showing evidence of severe hypertension or retinopathy and with renal function often returning toward or to normal levels. The most severe test which we have been able to devise was given the method, no patient being refused treatment because of severity of the disease. No other therapy was given. The expected mortality in malignant hypertension treated by conventional methods for one year is high. The seriousness of the disease present in this group of patients becomes manifest when each is graded according to the criteria of Smithwick which take into account secondary conditions due to atherosclerosis as well as cardiac and renal degeneration. All patients in stages IV and III were in Smithwick's groups 4 and 3. Of those in stage II, 20 were in group 3 and 2 in group 2. The mortality rates in patients treated medically in one year according to Smithwick are: group 4, 50.5 per cent; group 3, 17.2 per cent; group 2, 9.6 per cent. For surgically treated patients (lumbodorsal sympathectomy) they are: group
4, 23.6 per cent; group 3, 4.6 per cent; group 2, 3.3 per cent. Therefore, mortality rate in the present series of patients in his groups 4 and 3 treated by Hyphex up to two years is considerably lower than that of surgically treated patients, being 10.6 per cent for all causes of death, 5.8 per cent for those due to hypertension and uremia and 1.4 per cent for those due to hypertension without prior uremia.

Whether or not the course of benign hypertension is altered by control of the blood pressure will not be known until many years have elapsed. Experience has suggested, however, that some of the secondary effects of arterial hypertension may be prevented or postponed while others may not. For example, only two deaths from cerebral vascular accident have occurred, although 35 individuals had suffered one or more apoplectic strokes. No case of congestive heart failure has developed, nor has renal insufficiency appeared. From these relatively small numbers, we believe that cerebral arterial thrombosis may not be prevented, that renal insufficiency already present is often relatively intractable to treatment, but that cerebral hemorrhage, congestive heart failure, coronary occlusion and progressive renal damage may be postponed or prevented by control of the blood pressure. The basis for these beliefs will be presented in a subsequent communication. If an attempt to estimate the stage of hypertension now present in all individuals under adequate treatment were justifiable, 21 per cent would be in stage II (moderate benign), 53 per cent would be in stage I (mild benign), 21 per cent would be in stage 0 (prehypertensive), and 5 per cent would be normotensive. From another viewpoint, in every case the initial stage of the disease has regressed toward less severe ones, and in only 21 per cent (of stages II and III) has it failed to regress two or more stages.

It has been difficult to evaluate the results in this series of patients, which increased at the rate of about 12 a month, from the standpoint of duration of treatment. Over half have been taking Hyphex for a year or longer; they represent on the whole the more severe stages of the disease and its complications. In our experience, however, once control has been established for two or three months, it continues unless doses are altered or the patient fails to cooperate. Therefore, for the short term (25 months), tolerance to the drugs does not develop and progression of the primary disease is not to be expected unless renal insufficiency was present before treatment.

The method is by no means ideal. It represents a first approximation demonstrating that control is practical and feasible. Its hazards, both early and later, are discussed in the accompanying communication.

**Summary and Conclusions**

A method for the control of arterial hypertension has been developed and used for 6 to 25 months in 258 patients of whom 89 were in malignant, 5 in terminal uremic, and 130 in severe benign stages. Blood pressure fell in all cases and was maintained at reasonable levels in about 80 per cent. Tolerance did not develop when the method was strictly followed. The malignant stage was altered in all cases, but only three-fourths survived. The limiting factor of effectiveness appears to be in cases of renal insufficiency. Negroes on the whole did poorly. The method is practical for patients desirous of cooperating, when certain precautions are taken to prevent hypotension and obstipation.

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**Sumario Español**

Este informe es el primero de una serie sobre el método de tratamiento de la hipertensión con cloruro de hexametionium y hydrazinophthalazine. Cuando las drogas se tomaron estrictamente, la presión arterial se mantuvo a un nivel razonable o normal en 80 por ciento de
258 casos de hipertensión severa. El estado maligno cuando presente, fue reversado. La insuficiencia renal y aterosclerosis cerebral severa limitan la efectividad de este método de tratamiento para la prolongación de vida.

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