Further Observations on the Effects of Autonomic Blocking Agents in Patients with Hypertension

I. General Systemic Effects of Hexamethonium, Pentamethionium, and Hydrazinophthalazine

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Hexamethonium and pentamethonium produced a greater reduction in blood pressure in patients with malignant hypertension who had low serum concentration of sodium or severe encephalopathy than in those with benign hypertension. Concurrent administration of hydrazinophthalazine resulted in an additive effect on the blood pressure of most patients, with slower development of tolerance and less marked postural hypotension. In many patients there was improvement in signs and symptoms attributable to hypertension. Harmful effects of reduction in blood pressure occurred mainly in patients with malignant hypertension and consisted of renal insufficiency and evidence of myocardial and retinal ischemia.

Hexamethonium and pentamethonium [bis-trimethylammonium hexane (C-6) and pentane (C-5)] are quaternary ammonium compounds which are capable of blocking the transmission of nervous impulses across autonomic ganglia, both sympathetic and parasympathetic.

This action results in reduction in the blood pressure of recumbent hypertensive subjects, and of erect normotensive and hypertensive subjects. The daily oral or subcutaneous administration of these compounds is followed by some reduction in the blood pressure of most hypertensive patients and symptomatic improvement in many of these, but the degree and duration of this effect is limited by the development of tolerance. The concurrent administration of another antihypertensive drug, 1-hydrazinophthalazine (Apresoline), has been reported to have a synergistic effect, and to facilitate reduction of the blood pressure. Pentamethonium and hexamethonium have also been administered to normotensive subjects in order to increase blood flow to the extremities of patients with peripheral vascular disease, to reduce the secretion of gastric acid, and to produce postural hypotension and reduction of hemorrhage during certain operative procedures.

The studies to be reported here describe the effects of hexamethonium and pentamethonium administered intravenously to 72 hypertensive patients, and orally for several weeks to 30 of these. The effects of hydrazinophthalazine administered orally to 24 hypertensive patients, and in conjunction with hexamethonium to 16 of these for several months are also described. The effect of intravenous hexamethonium and pentamethonium on the blood pressure of 30 normotensive subjects is also reported.

Procedure

The hypertensive patients who were studied varied in age from 18 to 64 (average 42) years. The known duration of hypertension was 1 to 30 (average 6) years. All the patients had symptoms attributable to hypertension. The patients who are classified as having malignant hypertension are those who had marked and sustained elevation of blood pressure, and some degree of renal insufficiency, papilledema.

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and hypertensive encephalopathy. The range and average of the age and known duration of hypertension were approximately the same for the patients with benign and malignant hypertension.

In the large majority of observations the dichloride salts of hexamethonium and pentamethonium were employed, and in a smaller number the dibromide or di-iodide salts. The effective dose of these salts was dependent on the amount of methonium ion, and their effects were the same except for the occurrence of symptoms attributable to the accumulation of bromide ion in the few subjects who received protracted administration of the dibromide salt. The doses of methonium compound that are recorded are of the dichloride salt.

All observations on hypertensive patients were preceded by a period of at least one week of bed rest in the hospital. The methonium compounds were injected intravenously at an average rate of 3 mg. per minute until the blood pressure had fallen to normal or to levels intermediate between the original and normal, or until 108 mg. had been administered. The amount injected varied from 4 to 108 mg. (average 42 mg., or 0.6 mg. per kilogram). The blood pressure was determined by auscultation at intervals of one half to one minute during injection, and until the maximum fall was attained, after which measurements were made at longer intervals until the blood pressure had returned to near the original level. At varying intervals after injection, the effect of sitting, with the legs dangling over the sides of the bed, and of standing, was observed. Changes in posture were always active, rather than passive. Hexamethonium was administered orally several days after the intravenous injection, in an initial dose of 0.125 or 0.25 Gm., repeated at 8- to 12-hour intervals. The dose was progressively increased at intervals of one or more days by increments of 0.125 Gm., and the interval between doses shortened to six and then four hours, in an effort to maintain some degree of reduction in the blood pressure. The maximum daily dose was 9 Gm. In a few patients the effects of orally administered hexamethonium and pentamethonium were compared.

Several days after the cessation of hexamethonium, and after return of the blood pressure to the original elevated levels, hydrazinophthalazine was administered orally, in an initial dose of 25 mg., repeated at eight hour intervals. The dose was progressively increased at daily intervals by increments of 25 to 50 mg., and the interval between doses shortened to six and then four hours, in an effort to maintain some degree of reduction in the blood pressure. The maximum daily dose was 1 Gm. While the patients were receiving hydrazinophthalazine in average daily dose of 350 mg., hexamethonium was added, in an initial dose of 0.125 or 0.25 Gm. three times a day. The dose of hexamethonium was then gradually increased at intervals of one to several days in an effort to lower the blood pressure to normal or intermediate levels. This occurred at a daily dose of hexamethonium of between 0.7 and 6 Gm. (average 2.3 Gm.). The two drugs were administered at the same time and, whenever possible, before meals. In a few patients the sequence of drug administration was reversed.

All observations were carried out in the hospital, except for 10 patients who were given hexamethonium and hydrazinophthalazine for one to three months in the hospital, and were then followed in the outpatient department. During the patients' hospitalization the blood pressure, recumbent, was usually recorded prior to each dose of drug, and that recumbent and erect two hours after drug administration at least twice during the day. Following discharge from the hospital this was recorded from three times a day to once a week.

**Results**

**Effect of Intravenous Hexamethonium on Blood Pressure (Figs. 1 and 2)**

**Patients with Benign Hypertension.** The intravenous administration of 10 to 108 mg. (average 53 mg.) of hexamethonium to 41 patients with benign hypertension resulted in a reduction in the blood pressure, recumbent, to normotensive levels in 20 patients, to near normotensive levels (within 20 mm. Hg) in 11, and to levels intermediate between the original and normotensive in 8. In two patients there was no reduction in blood pressure following 108 mg. of hexamethonium. There was a
rough parallel between the effect of hexamethonium, in the doses administered, and the reduction in blood pressure that occurred during Sodium Amytal-induced sleep, except that the former was slightly greater in most patients. However, in two patients whose blood pressure did not fall during sleep, hexamethonium reduced the pressure to near normotensive levels. The effect of hexamethonium on the blood pressure was detectable within two or three minutes after injection of each increment, and was maximal within an average of nine minutes after the conclusion of the injection. In five patients the blood pressure fell appreciably during the half hour after termination of the injection. More rapid administration than 3 mg. per minute resulted in a somewhat greater reduction in blood pressure in most patients. In some patients increasing the dose of drug beyond that necessary to lower the blood pressure to normotensive levels resulted in only a slightly greater reduction in pressure, suggesting that a blood pressure “floor” had been reached, but in most patients a significantly greater fall in pressure occurred. In one patient progressive increases in the dose of hexamethonium resulted in lowering of the recumbent pressure to 95/56 mm. Hg. When hexamethonium was injected in equal doses on several occasions, there was usually some variation in the extent of the fall in blood pressure. The fall in systolic pressure was more rapid and about twice as great as the fall in diastolic pressure. The reduction in pressure was accompanied by only a slight increase in cardiac rate from an average of 87 to 94 per minute. In all patients there was marked postural hypotension, the pressure falling to an average of 104/76 after one half to two minutes of standing, with the systolic pressure falling more rapidly than the diastolic. The postural hypotension was accompanied in most patients by symptoms of syncope, including giddiness, sometimes nausea, vertigo, scotomata, tinnitus, faintness, pallor, deep sighing respirations, and yawning. Postural hypotension also occurred after the injection of small doses of drug which had little or no effect on the pressure, recumbent. The marked reduction in blood pressure that occurred on standing was accompanied by only slight acceleration of cardiac rate, to an average of 101 per minute, which was only slightly greater than the average rate on standing prior to hexamethonium (98 per minute). When the recumbent position was resumed the blood pressure rose immediately to, or slightly above, the level prior to standing, and the cardiac rate became slightly slower than the rate prior to standing. The pressure, recumbent, gradually returned to the initial level over a period of 2 to 24 (average 5) hours, while the postural hypotension diminished more slowly (average duration 7 hours). The length of time that the patients could stand before the blood pressure fell varied with the time that had elapsed since the injection of drug.

Patients with Malignant Hypertension. The intravenous administration of 5 to 80 mg. (average 29 mg.) of hexamethonium to eight patients with malignant hypertension resulted in a reduction in pressure to below normal in two patients, to normal levels in four, to near normal in one, and to a level intermediate between the original and normotensive in one. In all except the latter patient, the fall in pressure was considerably greater than that which had occurred during sodium amytal induced sleep. Reduction in blood pressure to shock levels was accompanied by an increase in average cardiac rate of 27 per minute, and lesser reduction in blood pressure by an average increase of 5 per minute. In six patients marked fall in pressure was accompanied by symptoms of syncope. The blood pressure increased slightly on elevation of the lower extremities, and returned to or near the original level over a period of three to nine (average five) hours. Marked postural hypotension was present in all the patients when they were allowed to sit or stand up following partial recovery of the blood pressure, recumbent.

Patients with Chronic Glomerulonephritis and Hypertension. The intravenous administration of 10 mg. of hexamethonium resulted in a marked reduction in pressure to below normal in one patient, while the administration of 50 mg. to another patient resulted in a moderate reduction, to normal. In the former patient the reduction in pressure was much greater than that which occurred following sodium
Amytal, while in the latter it was slightly greater.

Influence of Nitrogen Retention, Low Serum Sodium Concentration, Low Dietary Intake of Sodium, and Presence of Hypertensive Encephalopathy on Effect of Intravenous Hexamethonium. None of the patients with benign hypertension had nitrogen retention, low serum sodium concentration, or encephalopathy, and none had a drastic fall in blood pressure, recumbent, following the intravenous administration of less than 85 mg. of hexamethonium. All of the eight patients with malignant hypertension had nitrogen retention and encephalopathy, and six of them had a marked fall in

blood pressure, recumbent, following the injection of less than 18 mg. of hexamethonium (fig. 2). Of these six patients, four had low serum sodium concentration. The other two patients were distinguished only by the presence of the most marked encephalopathy observed in this group. Of two patients with chronic glomerulonephritis and uremia who were studied, one, whose serum sodium concentration was low, was extremely responsive to a small dose of hexamethonium, while the other patient, whose serum sodium concentration was normal, showed a relatively small response to a much larger dose. The effect of hexamethonium appeared to be prolonged in the patients with renal insufficiency, but increased response to a single injection was observed only when the renal insufficiency was associated with low serum sodium concentration or severe encephalopathy.

When the daily dietary intake of sodium chloride was increased from 1 to 4 Gm. in one of the patients with malignant hypertension who had a low serum sodium level and a marked response to a small dose of hexamethonium, there was a striking diminution in response to the drug, coincident with an increase in the serum sodium level (fig. 3). In two pa-

patients with benign hypertension the response to hexamethonium or pentamethonium was increased following reduction of sodium chloride intake and injection of mercurial diuretic, although the serum sodium level was not altered (fig. 3). The response was also considerably increased following onset of subarachnoid hemorrhage in one other patient and of cerebral vascular accident, with coma, in another.

Normotensive Subjects. The intravenous administration of 20 to 50 mg. (average 30 mg.) of hexamethonium produced a slight to moder-
ate reduction in the blood pressure, recumbent, by 8/0 to 40/20 mm. Hg (average 21/10) in 29 of 30 subjects. This was accompanied by an average increase in cardiac rate of 8 per minute. On standing there was a marked fall in blood pressure within one to three minutes, to 80/60 or below, with syncope. The cardiac rate increased only slightly on standing by an average of 6 per minute. The effect of resuming the recumbent position, and the duration of the postural hypotension, were similar to that observed in the hypertensive subjects.

In one normal subject the intravenous injection of 25 mg. of hexamethonium at 3 mg. per minute resulted in a fall in the blood pressure, recumbent, from 130/90 to 70/50. The cardiac rate did not change. The blood pressure was not altered by elevation of the lower extremities. The administration of 0.25 mg. of adrenaline subcutaneously resulted in transient elevation of the blood pressure to 240/100, but within 10 minutes the pressure was again subnormal. Following 20 mg. Vasoxyl (methoxamine hydrochloride) intramuscularly the blood pressure gradually returned to the original level over a period of 40 minutes. Injection of 0.25 mg. of adrenaline several weeks later had little effect on the blood pressure.

Effect of Oral Hexamethonium on Blood Pressure (Fig. 4)

Patients with Benign Hypertension. The response to the initial oral doses paralleled in general the response to approximately one-twentieth as much drug administered intravenously, and also paralleled roughly the response to sodium amytal. During the first four days of oral administration of 0.5 to 3 (average 1.3) Gm. a day the blood pressure, recumbent, fell to normal levels in three patients, to near normal in five, and to intermediate levels in eight. The systolic pressure was usually reduced to a greater extent than the diastolic. In two patients there was no reduction in recumbent pressure. The average blood pressure declined from 213/126 to 167/103. In 16 of the 18 patients there was further reduction in pressure on standing to, or below, normotensive levels. The postural hypotension diminished with activity or following the application of an abdominal binder or of pressure bandages to the lower extremities. It was most marked on motionless standing immediately after getting up from the recumbent position or following exercise. Most patients had to lie down at times because of syncope. There was considerable fluctuation in the blood pressure, both recumbent and erect, during a 24-hour period, even when hexamethonium was administered at four hour intervals. The average cardiac rates, recumbent and erect, were the same as prior to hexamethonium administration (80 and 98 per minute).

During 1 to 25 weeks (average 4 weeks) of administration of hexamethonium the response to the drug gradually diminished, and the daily dose had to be increased to an average of 4 Gm., and as high as 9 Gm. in two patients, in order to maintain any reduction in the blood pressure. Two patients continued to have no reduction in blood pressure while recumbent, in spite of increased intake of drug. The blood pressure, recumbent, was maintained at normal levels in only one patient, near normal in three, and at intermediate levels, particularly with regard to the systolic pressure, in six. It returned to the original level in six patients. The average blood pressure, recumbent, during the fourth week of drug administration was 179/104. Postural hypotension disappeared in two patients, increased in two, and diminished in the remainder. In eight patients, the erect
blood pressure continued to be at or near normotensive levels, while in eight patients it was intermediate between the original and normotensive. The pressor response to cold, emotional stimuli, and intravenous histamine was only slightly to moderately diminished, and elevation of the blood pressure to hypertensive levels occurred following these stimuli. In one patient who developed tolerance to large oral doses of hexamethonium there was a marked decrease in the response to large intravenous doses of either hexamethonium or pentamethonium (fig. 5). The response returned between 4 and 17 days after cessation of oral administration. The development of tolerance to hexamethonium was also observed following intramuscular administration at six hour intervals for periods of 3 to 10 weeks. Moderate response to the drug returned within seven days after cessation of administration.

**Patients with Malignant Hypertension.** The initial reduction of blood pressure was somewhat greater in most of these patients than in those with benign hypertension, the blood pressure falling in response to smaller doses of hexamethonium. This paralleled their response to intravenous hexamethonium (in doses about one twentieth as great), and was, in most instances, considerably greater than their response to sodium amytyl. Four patients had a marked reduction in pressure to or near normotensive levels during the first three days of oral administration, five patients had reduction to levels intermediate between the original and normotensive, and one patient had no reduction in pressure.

Of the patients who had the greatest initial response to small oral doses of hexamethonium, two had low concentration of serum sodium, and these two patients and two others had the most marked hypertensive encephalopathy. In spite of their initial responsiveness to small oral doses of hexamethonium, and in spite of the presence of low serum sodium concentration and of hypertensive encephalopathy, tolerance to the drug appeared in the malignant hypertensives just as rapidly as in the patients with benign hypertension. During the first two weeks of daily oral administration the blood pressure rose progressively, in spite of a four fold increase in the daily dose of hexamethonium. In four patients the blood pressure returned to the original levels, while in four it rose to levels intermediate between the original and normotensive. Alterations in the erect blood pressure and in recumbent and erect cardiac rates were the same as in the patients with benign hypertension.

**Patients with Chronic Glomerulonephritis.** The response to oral hexamethonium paralleled that to intravenous administration (fig. 2) in the two patients who were studied. One patient (S. B.), who had low concentration of serum sodium, had a marked reduction in blood pressure to below normal after only 0.12 Gm. of hexamethonium orally. The other patient had a moderate reduction in pressure to normal levels, and moderate postural hypotension, during a 10-day period of oral administration of 1 to 2 Gm. of hexamethonium daily.

**Effect of Pentamethionium on Blood Pressure**

Intravenous pentamethionium had the same effect as hexamethionium in both normal and hypertensive subjects (fig. 1). Oral pentamethionium had slightly less effect on the recumbent and erect blood pressure than hexamethionium. The development of tolerance to either drug was accompanied by tolerance to the other.
whether administered orally or intravenously (fig. 5).

**Potentiation of the Hypotensive Effect of Other Vasodilator Drugs by Hexamethonium**

During the daily oral administration of hexamethonium or pentamethonium there was an increase in the hypotensive effect of other vasodilator drugs, such as nitroglycerin, erythritol tetranitrate, and hydrazinophthalazine, administered orally. The effect of the former two drugs and hexamethonium on the recumbent and erect blood pressure was more than additive, while the effect of hydrazino-

phthalazine and hexamethonium was usually additive (figs. 6 and 7).

**Effect of Sympathectomy on Response to Hexamethonium**

Hexamethonium was administered intravenously and orally to four patients (two with benign and two with malignant hypertension) prior to lumbodorsal sympathectomy, and one half, one, two, and three years after sympathectomy, at which time the recumbent blood pressure had returned to or near the original level. The initial response of these patients to hexamethonium was greater following sympathectomy, but the rate of development of tolerance appeared to be unchanged.

**Lack of Correlation between the Effect of Methonium and of Lumbodorsal Sympathectomy on Blood Pressure**

Six patients who had received intravenous hexamethonium or pentamethonium were later subjected to lumbodorsal sympathectomy. In five of these, the recumbent blood pressure was reduced to or near normotensive levels by methonium, while the sixth patient had no fall in pressure following 108 mg. of hexamethonium. All had marked postural hypotension. Two weeks after sympathectomy the recumbent pressure of all six patients was at or near normal levels, and all had marked postural hypotension. Nine months later the recumbent pressure of five patients had returned to or near the original level, while that of one patient remained normal. Three patients had normal pressure on standing, while in three the pressure fell to levels intermediate between the hypertensive recumbent level and normal.

**Effect of Oral Hydrazinophthalazine on Blood Pressure (Figs. 6 and 7)**

This drug was administered to 16 patients with benign hypertension and eight with malignant hypertension for an average period of 12 days. The doses that were administered resulted in a moderate reduction of recumbent...
pressure in 14 patients (9 benign and 5 malignant hypertensives) to levels intermediate between the original and normotensive, and no significant reduction in 10 patients. In two patients with malignant hypertension the blood pressure fell transiently to near normal correlation with the reduction in blood pressure that occurred during Sodium Amytal–induced sleep. The average pressure, erect, was only slightly lower than that recumbent, and marked postural hypotension was not observed. In some patients the effect of the drug on the blood pressure diminished during the brief period of observation, but this development of tolerance was less marked than following hexamethonium. Hydrazinophthalazine produced slight to moderate cardioacceleration, even in some of the patients who had little or no fall in blood pressure, the average rate increasing from 86 to 97 per minute. On standing the average cardiac rate increased to 110 per minute.

**Effect of Oral Hydrazinophthalazine on Blood Pressure Response to Intravenous Hexamethonium (Fig. 8).** Hexamethonium was administered intravenously to five patients with benign hypertension and one with malignant hypertension before and during the daily oral administration of hydrazinophthalazine. In five patients whose blood pressure had been lowered to some extent by oral hydrazinophthalazine, the blood pressure was reduced to lower levels by intravenous hexamethonium than had been the case prior to hydrazinophthalazine administration. In two patients the effect on
the blood pressure was additive, while in three others it was more than additive. The potentiation of the hypotensive action of hexamethonium by hydrazinophthalazine was most marked in the patient with malignant hypertension. In the sixth patient, whose blood pressure rose slightly during hydrazinophthalazine administration, the pressure fell to the same normotensive level after each injection of hexamethonium.

The potentiation of the hypotensive action of hexamethonium by hydrazinophthalazine was most marked in the patient with malignant hypertension. In the sixth patient, whose blood pressure rose slightly during hydrazinophthalazine administration, the pressure fell to the same normotensive level after each injection of hexamethonium.

**Effect of the Concurrent Oral Administration of Hydrazinophthalazine and Hexamethonium on Blood Pressure (Figs. 6, 7, 9 and 10)**

This was studied in 10 patients with benign hypertension and six with malignant hypertension, following a period of observation of the effect of hexamethonium and of hydrazinophthalazine administered separately. The former drug was usually administered first, in order to allow a sufficient time interval between the two courses of hexamethonium for tolerance to this compound to diminish. Hexamethonium alone produced a moderate lowering of blood pressure to levels intermediate between the original and normotensive in eight patients (four benign and four malignant), and a slight reduction in eight patients. All but two of the patients had mild or moderate postural hypotension. Hydrazinophthalazine alone produced a moderate or slight lowering of pressure in the same number of patients. Concurrent administration of the two drugs resulted, during the first two to four weeks, in reduction in the blood pressure, recumbent, to or near normotensive levels in eight patients (five benign and three malignant), and to levels intermediate between the original and normotensive in eight patients (five benign and three malignant). In the patients with malignant hypertension smaller doses of drugs were required to lower the pressure than in those with benign hypertension. The reduction in systolic pressure was greater than the reduction in diastolic pressure. With continued administration for 2 to 40
(average 18) weeks the blood pressure rose to a moderate degree in eleven patients, in spite of an average increase of 60 per cent in the daily dose of both hexamethonium and hydrazinophthalazine. In three patients the blood pressure returned to near the original levels, while in 12 patients the blood pressure was maintained at levels intermediate between the original and normotensive. The development of tolerance was slower and less marked than during the administration of hexamethonium alone. In most patients there were fairly wide fluctuations in blood pressure throughout the day (fig. 9); it was not unusual for the blood pressure to be normotensive at some times, and near the original elevated level at other times, especially following emotional stress. The response to the cold pressor test was only slightly diminished. In four patients the response to the drugs increased after several weeks, and the dose of hexamethonium had to be reduced (fig. 10). All the patients had moderate or severe postural hypotension during the first week of addition of hexamethonium to hydrazinophthalazine. This was most marked immediately on rising from the recumbent position, and usually diminished on walking about. With continued administration of these drugs the postural hypotension diminished in severity in all patients, and disappeared in 10, except for brief periods following increases in the intake of hexamethonium. In four patients postural hypotension recurred follow-

Fig. 10. Effect of oral hydrazinophthalazine, hexamethonium, and hexamethonium plus hydrazinophthalazine on the recumbent and standing blood pressure of a patient with benign hypertension.

ing exercise, sweating, or diarrhea, or during very hot weather. One patient had no postural hypotension while he was engaged in office work, but did have this when he relaxed at home. In general, postural hypotension was less marked during combined drug administration than during hexamethonium alone, and the same degree of postural hypotension was usually accompanied by a somewhat greater increase in cardiac rate, and by less marked symptoms of syncope. Nevertheless, it was very difficult, even in the more responsive patients, to lower the recumbent blood pressure to normotensive levels without producing intermittent syncope on standing.

During hydrazinophthalazine administration less hexamethonium was required for comparable reduction in pressure than when hexamethonium was administered alone. The effect of combined administration of the drugs on the blood pressure was approximately additive in 12 patients, greater than additive in two, and less than additive in two.

When administration of the drugs, or of their combination, was discontinued postural hypotension disappeared within one to two days and the recumbent blood pressure rose within two to five days to or above the original level. When drug administration was resumed, smaller doses were initially required for reduction of the blood pressure than at the time of cessation of administration.

The degree of lowering of the blood pressure could not be correlated with the dietary intake of sodium chloride, which was 1 to 4 (average 3) Gm. a day. When tolerance to hexamethonium or to hexamethonium plus hydrazinophthalazine had developed the dietary intake of sodium chloride was reduced in some patients, to as low as 0.5 Gm. a day. In several instances, prolonged restriction of sodium chloride intake increased the response to drug administration to some extent, and appeared to delay, though it did not prevent, the development of tolerance.

Cardiac Rate. The average cardiac rate was 78 (recumbent) and 87 (erect) during the control period and during hexamethonium administration, 93 and 105 during hydrazino-
Effects of Reduction in Blood Pressure by Oral Hexamethonium, Hydrazinophthalazine, and Hexamethonium Plus Hydrazinophthalazine

Effect of Signs and Symptoms Attributable to Hypertension (Table 1). The degree of amelioration of the signs and symptoms attributable to hypertension depended in part on the degree and duration of the reduction in blood pressure, and was more notable following combined drug administration than following either drug alone. Improvement occurred after moderate reduction in pressure to intermediate levels, as well as after reduction to near normal. Headache was the symptom most commonly improved. The most dramatic improvement noted was in the signs and symptoms of hypertensive encephalopathy. These improved in five patients with malignant hypertension within a few days after lowering of the blood pressure, and remained so as long as the blood pressure was maintained at reduced levels, over a period of one to eight months. One other patient showed no improvement, and one became worse following reduction in the blood pressure to near normal. One patient who had had a subarachnoid hemorrhage improved rapidly following reduction in blood pressure. Exertional dyspnea and orthopnea diminished in several patients, and left ventricular enlargement, palpitation, weakness, giddy spells, and recurrent epistaxes diminished in a few. Retinal hemorrhages, exudates and papilledema improved in approximately half the patients in whom these changes were present, but vision improved in a smaller number. In two patients with malignant hypertension and severe retinopathy there was transient loss of vision following reduction in the blood pressure to normal, but vision returned when the blood pressure rose to intermediate levels.

Effect on the Electrocardiogram. Of 30 patients studied, 22 had abnormal electrocardiograms (19 left ventricular "strain" pattern, two nonspecific T-wave abnormalities, and one left bundle branch block), five had borderline records (left axis deviation and minor T-wave changes), and three had normal records. None of the patients had symptoms or electrocardiographic changes suggestive of coronary insufficiency, as this was regarded as a contraindication to drug administration. Following reduction in blood pressure by hexamethonium or hexamethonium plus hydrazinophthalazine there was moderate improvement in the electrocardiograms of two patients, consisting of disappearance of left ventricular "strain" pattern in one and replacement of left bundle branch block by left ventricular strain in the other, minor improvement in seven, consisting of changes in the

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S-T segments and T waves, no change in 19 patients, and worsening of the electrocardiogram in two patients. There were no significant changes in the QRS axis. None of the abnormal electrocardiograms, and only one of the borderline records, became normal. The two patients who had worsening of the electrocardiogram following reduction in blood pressure were malignant hypertensives, 27 and 44 years of age, whose electrocardiogram had revealed only left axis deviation prior to drug administration. Following gradual reduction in blood pressure from 240/150 to 140/110 by the oral administration of 0.5 to 1 Gm. of hexamethonium a day for four days, both patients experienced slight discomfort over the precordium, and were found to have electrocardiographic changes consisting of increased depression of the S-T segments and sharp inversion of the T waves in the first and second limb and fifth precordial leads. Hexamethonium administration was stopped, following which the blood pressure promptly returned to the original level in the 27 year old patient, and the electrocardiographic changes disappeared in this patient over a period of two weeks. In the other patient (D. M., fig. 11) the blood pressure was unchanged following cessation of hexamethonium, and the electrocardiographic changes became more marked. On the fifth day after cessation of drug there was a further fall in blood pressure, and the patient died after futile attempts to raise the blood pressure by means of shock position and intravenous infusion of saline, glucose, and norepinephrine. Except for this evidence of coronary insufficiency in one patient, and of probable myocardial infarction in another, the electrocardiographic changes observed in the patients with malignant hypertension were similar to those in the patients with benign hypertension. The minor improvement that occurred in some patients could not be correlated with the precise degree or duration of reduction in blood pressure, with the age of the patient, or with the known duration of hypertension. The addition of hydrazinophthalazine did not have any definite influence on the effect of hexamethonium on the electrocardiogram, except to increase the cardiac rate in some patients.

In two patients, one of whom had benign and one malignant hypertension, reduction of the blood pressure by oral hydrazinophthalazine alone to near normotensive levels resulted in nausea and substernal discomfort, deep cove-shaped inversion of the T waves in the second and third limb and fifth precordial leads in one patient, and depression of the S-T segments in the first and second limb and fifth precordial leads in the other patient. These changes, which are compatible with myocardial ischemia or infarction in the former patient, and with coronary insufficiency in the latter, progressed in spite of cessation of drug administration and prompt return of the blood pressure to the original elevated level. The electrocardiogram gradually returned to its original form over a period of two weeks, except for persistence of deep inversion of the T wave in the fifth precordial lead.

Effect on Renal Function: In Patients with Benign Hypertension. These had normal blood nonprotein nitrogen concentration and normal or slightly depressed phenolsulfophthalein excretion prior to drug administration. There was no significant change in these determinations when the blood pressure was lowered.

In Patients with Malignant Hypertension. Of the 10 who received hexamethonium, one (R. C., fig. 11) had normal excretion of phenolsulfophthalein and normal blood nonprotein nitrogen concentration, while the remainder had slightly to moderately decreased excretion of phenolsulfophthalein and slightly elevated blood nonprotein nitrogen. In the former patient and in three of the latter the oral administration of hexamethonium resulted in marked elevation of the blood nonprotein nitrogen concentration following reduction in the recumbent blood pressure to near normotensive levels. The course of three patients is charted in figure 11. In the fourth patient the blood nonprotein nitrogen rose from 64 to 140 mg. per 100 cc. following reduction of the recumbent blood pressure to near normal by 0.5 to 1 Gm. of hexamethonium daily by mouth for three days. In spite of the cessation
of hexamethonium administration in each instance, and return of the blood pressure to or near the original elevated levels in three of the four patients, nitrogen retention progressed and all died in uremia. Postmortem examination performed in two patients showed severe intrarenal arteriosclerosis, scattered necrotic intraglomerular arterioles, and filling of the renal tubules with acellular material. Of the six other patients four had slight to moderate reduction in recumbent pressure during oral hexamethonium administration and two had reduction to near normotensive levels, with no alteration in blood nonprotein nitrogen concentration.

The oral administration to six patients of short courses of hexamethonium and of hydrazinophthalazine followed by prolonged courses of the two drugs administered together resulted in slight elevation of blood nonprotein nitrogen during hexamethonium in one patient and during combined drug administration in another, and slight lowering of phenolsulfonphthalein excretion during combined drug administration in two patients. In spite of the greater and more prolonged lowering of blood pressure during combined drug administration than during hexamethonium alone none of the patients developed progressive nitrogen retention during the former.

In no patient did the administration of hexamethonium, hydrazinophthalazine, or both result in any improvement in renal function, as reflected by the concentration of blood nonprotein nitrogen and by the phenolsulfonphthalein excretion.

**Patients with Chronic Glomerulonephritis.**

In two patients with marked renal insufficiency reduction of blood pressure to normotensive levels for relatively brief periods by hexamethonium resulted in only slight transient elevation of nonprotein nitrogen and reduction in phenolsulfonphthalein excretion.

**Occurrence of Hemodilution Following Reduction in Blood Pressure by Hexamethonium, Hydrazinophthalazine, or Both.**

In four patients there was moderate reduction in the hematocrit and red blood count during hexamethonium administration, and in three patients during combined hexamethonium and hydrazinophthalazine. The average hematocrit of these patients was 42 per cent prior to, and 32 per cent after 5 to 12 days of drug administration. In one patient the hematocrit fell during each of two courses of hexamethonium. All the patients had reduction in the recumbent blood pressure to normotensive or intermediate levels, and postural hypotension, during the period of drug administration. Five of the eight patients had malignant hypertension, with some reduction in renal function, but with little or no elevation in the concentration of blood nonprotein nitrogen. In only one patient did the latter increase during drug administration, and this occurred only during the second of two courses. In two patients less marked reduction in the hematocrit and red blood count occurred during 10 days of hydrazinophthalazine administration, the hematocrit falling from 46 per cent to 40 per cent.

Determination of serum protein concentration was performed in only two patients. In both of these, reduction in the concentration of total protein, albumin, and globulin, and in the activity of serum cholinesterase, occurred coincident with and proportionate to the reduction in the hematocrit. In two other patients extracellular fluid volume was determined from the volume of distribution of inulin, and was found to be increased from 11 and 15 liters to...
14 and 18 liters, coincident with the reduction in the hematocrit. In spite of the occurrence of hemodilution, and presumably of increased plasma volume as well as of increased extracellular fluid volume, mild pretibial edema was observed in only three patients, and none developed frank signs of cardiac failure. The daily intake of sodium chloride was 1 to 4 (average 2.9) Gm., and was the same during as prior to drug administration. In five patients there was a slight increase in the serum sodium concentration during drug administration, from an average of 134 mEq. per liter to 140 mEq. per liter, but in the other three patients there was no change. There was no alteration in the red blood cell indexes, and no evidence of increased hemolysis. Smears of the bone marrow of two patients were normal.

Continued administration of hexamethonium did not result in further reduction in the hematocrit; in some instances, the hematocrit returned to the original level as the blood pressure rose with the development of tolerance to the drug. Cessation of hexamethonium resulted in rapid return of blood pressure and hematocrit to their original levels. None of the patients who developed rapid tolerance to the drugs, and whose blood pressure did not fall during administration of as much as 9 Gm. of hexamethonium a day, and 800 mg. of hydrazinophthalazine a day, had any reduction in the hematocrit, in the concentration of serum albumin or globulin, or in the activity of serum or red blood cell cholinesterase.

**Other Effects of Hexamethionium (Table 2)**

The intravenous or oral administration of hexamethonium or pentamethonium resulted in other evidences of autonomic blocking action, in addition to reduction in the recumbent blood pressure and postural hypotension. In most patients there was initially mild dryness of the mouth, slight blurring of vision, constipation, and increased temperature of the extremities, sometimes associated with chilly sensations. Some patients also had slight pupillary dilation, gastric dilatation, anorexia, transient nausea and vomiting, a bitter taste in the mouth, and urinary hesitancy and retention. These effects were rarely severe enough to require any therapeutic measures, and they usually diminished coincident with the development of tolerance to the hypotensive effect of the drug. The constipation could usually be alleviated by laxatives and enemas. Rarely, gastric dilatation, abdominal distention, or urinary symptoms required treatment. These effects could be

**Table 2.—Side Effects of Oral Hexamethionium in 30 Hypertensive Patients**

<table>
<thead>
<tr>
<th>Effects Attributable to Ganglionic Blockade</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>12</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia and nausea</td>
<td>6</td>
</tr>
<tr>
<td>Eructation and bitter taste</td>
<td>2</td>
</tr>
<tr>
<td>Gastric dilation</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
</tr>
<tr>
<td>Dry mouth and throat</td>
<td>7</td>
</tr>
<tr>
<td>Blurred near vision</td>
<td>7</td>
</tr>
<tr>
<td>Dilated pupils</td>
<td>5</td>
</tr>
<tr>
<td>Urinary hesitancy</td>
<td>2</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2</td>
</tr>
<tr>
<td>Decreased potentia</td>
<td>3</td>
</tr>
<tr>
<td>Increased warmth of extremities</td>
<td>4</td>
</tr>
<tr>
<td>with subjective warmth</td>
<td>1</td>
</tr>
<tr>
<td>with subjective chilliness</td>
<td>2</td>
</tr>
</tbody>
</table>

**Effects which May be Due to Central Action**

| Drowsiness, lethargy, weakness            | 8                  |
| Paresthesias of mouth, tongue, and extremities | 1            |

**Other Effects**

| Diarrhea                                  | 2*                 |
| Reduction in hematocrit                   | 6*                 |

* Two patients were also receiving hydrazinophthalazine.

alleviated by the oral administration of 5 to 10 mg. of urecholine, or by the intramuscular administration of 1 mg. of Neostigmine or of 2 mg. of di-isopropyl fluorophosphate (DFP), followed by 0.5 to 1 mg. of Neostigmine and 10 to 20 units of pitressin. Three patients complained of diminished potentia during the first few weeks of oral hexamethonium administration. Eight patients complained of drowsiness, lethargy, and subjective weakness. These symptoms were mild in all but one patient whose daily intake of hexamethonium
could not be increased above 3 Gm. a day without the occurrence of moderately severe drowsiness. The drowsiness and lethargy would appear to be referable to a direct effect of methonium on the central nervous system, since these symptoms occurred in some patients following little or no reduction in blood pressure. Subjective weakness occurred concomitant with these symptoms in some patients, but also occurred in their absence following reduction in the blood pressure.

Table 3.—Side Effects of Oral Hydrazinophthalazine in 24 Hypertensive Patients

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7</td>
</tr>
<tr>
<td>Pain in back of neck, shoulders, arms</td>
<td>3</td>
</tr>
<tr>
<td>Rhinitis, conjunctivitis, lacrimation, photophobia, periorbital edema</td>
<td>4</td>
</tr>
<tr>
<td>Hiccups</td>
<td>2</td>
</tr>
<tr>
<td>Giddiness in absence of fall in blood pressure</td>
<td>2</td>
</tr>
<tr>
<td>Substernal discomfort in absence of fall in blood pressure</td>
<td>2</td>
</tr>
<tr>
<td>Subjective warmth</td>
<td>1</td>
</tr>
<tr>
<td>Pain in flanks</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>Weakness</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
</tr>
<tr>
<td>Reduction in hematocrit</td>
<td>2</td>
</tr>
</tbody>
</table>

Other Effects of Hydrazinophthalazine (Table 3)

Seven patients developed severe headache and four conjunctivitis, lacrimation, periorbital edema, and coryza. In two patients, one of whom was also receiving hexamethonium, this was associated with severe and protracted hiccups, and in one of these with fever. These effects subsided promptly following discontinuation of the drug. In one patient they did not recur when hydrazinophthalazine was resumed. Other effects are recorded in Table 3.

The headache, conjunctivitis, and coryza that may occur during hydrazinophthalazine administration have been ascribed by some to histamine released as a result of the purported antihistaminase activity of hydrazinophthalazine. However, measurement of the daily urinary excretion of acetyl histamine, and of the local wheal and flare produced by graded dilutions of intradermal histamine, revealed no change during drug administration.

Discussion

The oral or intravenous administration of hexamethonium or pentamethonium produced an initial moderate reduction in blood pressure in a majority of hypertensive patients, but continued oral administration resulted in diminished response to either drug. Moderate reduction in recumbent blood pressure by the oral administration of these compounds could be achieved for more than a few days in only a few patients. The initial response to the drugs, administered orally or parenterally, was greatest in those patients (mainly those with malignant hypertension) who had either marked encephalopathy or reduced concentration of sodium in the serum. The cause of the increased reactivity to methonium observed in these patients is not known, although, in the latter patients, associated reduction in plasma volume may have played a part.

The effects of methonium salts could largely be interpreted in terms of the effects of inhibition of ganglionic conduction, including reduction of sympathetic vasoconstrictor tone and partial inhibition of reflexes mediated through the sympathetic and parasympathetic nervous systems. The inhibitory effect of methonium appeared to be more notable on whichever division of autonomic activity is normally greater; for example, parasympathetic in the case of the smooth muscle of the iris, gastrointestinal tract, and bladder, and sympathetic in the case of smooth muscle of the peripheral vascular tree. However, the hypotensive effects of methonium were not always entirely explicable in terms of reduction in sympathetic vasoconstrictor tone alone. Although sympathetic vasoconstrictor tone is believed to make a greater contribution to the elevation of the blood pressure of patients with benign hypertension than of those with malignant hypertension, as reflected by the response to sodium amytal induced sleep, it
was the latter patients who had the more marked initial response to methonium.

After several days of methonium administration tolerance usually developed not only to the effect of the drug on the blood pressure, both recumbent and erect, but also to the other effects attributable to the inhibition of autonomic reflexes, and to the central effects. The mechanism of this tolerance is not known. The observation of hemodilution and of increased extracellular volume following the initial reduction in blood pressure suggests that this reduction may have resulted in increased retention of sodium. Such retention might result in a decrease in the hypotensive effect of methonium. However, while rigid restriction of sodium chloride intake usually delayed the development of tolerance, it did not prevent it, and rapid development of tolerance was observed even in patients whose sodium chloride intake was very restricted, and it was observed in the absence of hemodilution. Therefore it seems likely that other factors are more important in the development of tolerance. The suggestion has been made that decreased absorption of methonium from the intestine may play a part, but this could not explain the development of tolerance to parenterally administered drug. The increased hypotensive response to methonium that occurred following the onset of hypertensive encephalopathy or of cerebral vascular accident indicates that the central nervous system may play an important role in influencing reactivity to methonium.

Hydrazinophthalazine produced a slight to moderate reduction in blood pressure in about half the patients who were studied, and, when this drug was administered concurrently with hexamethonium, the reduction in pressure was greater than following either drug alone and tolerance appeared to develop more slowly. These observations are in conformance with those of Fries10 and Schroeder.11 In most patients the effect of the two drugs on the blood pressure appeared to be approximately additive. Following comparable reduction in recumbent blood pressure there was less marked postural hypotension during combined drug administration than during hexamethonium alone, and similar degrees of postural hypotension appeared to be somewhat better tolerated. These effects of combined drug administration may be due to the effect of hydrazinophthalazine in reducing hexamethonium requirement and in increasing cardiac output by increasing cardiac rate, and, as has been demonstrated following intravenous administration,19 by increasing stroke volume. The latter effect may be particularly important, since moderate or marked reduction in recumbent pressure by (intravenous) methonium is accompanied by a reduction in stroke volume and cardiac output,29 probably owing to decreased venous return to the heart resulting from pooling of blood in the peripheral circulation. The reduction in stroke volume and cardiac output becomes even more marked when the blood pressure falls further on standing.

Even during combined drug administration, it was seldom possible to lower the recumbent blood pressure to consistently normal levels without producing intermittent severe postural hypotension. However, moderate reduction in recumbent pressure, to levels intermediate between the original and normotensive, could usually be achieved with only occasional marked postural hypotension. This moderate reduction in recumbent pressure was sufficient to produce improvement in many of the signs and symptoms attributable to hypertension, particularly those attributable to hypertensive encephalopathy, and to a lesser degree, retinopathy and left ventricular strain.

Following reduction in pressure to or near normal by oral hexamethonium a marked decrease in renal function occurred in four patients, electrocardiographic changes compatible with coronary insufficiency occurred in two, transient loss of vision in two, and increased encephalopathy in one. All of these patients had malignant hypertension. Since untoward effects of reduction in blood pressure were noted mainly in the patients with malignant hypertension, it would appear that the danger of reduced blood flow to the kidneys, heart, retina, and brain is greater in these patients, who probably have a greater degree of fixed vascular change, than in patients with
benign hypertension. The progression of renal insufficiency to uremia in spite of discontinuation of drug administration and return of the elevated blood pressure indicates that transient reduction in blood pressure by hexamethonium may lead to irreversible renal changes in patients with malignant hypertension. In almost all the patients who were studied, the occurrence of syncope during postural hypotension indicated transient reduction in cerebral blood flow at this time.

Following moderate reduction in blood pressure by hydrazinophthalazine, symptoms and electrocardiographic changes compatible with coronary insufficiency occurred in one patient with benign hypertension and in one with malignant hypertension. None of the patients who were studied developed more than mild and transient evidence of reduction in renal function following reduction in blood pressure by hydrazinophthalazine, or by this drug plus hexamethonium. Intravenous hydrazinophthalazine has been found to increase renal blood flow in many hypertensive patients. Oral hydrazinophthalazine did not significantly increase renal blood flow, but it did appear to lessen the effect of reduction in blood pressure by intravenous hexamethonium on renal blood flow, and, to a lesser extent, on glomerular filtration rate. While observations on the clinical effects of these compounds in a larger number of patients will be necessary to confirm the apparent action of hydrazinophthalazine in reducing the incidence of renal insufficiency during hexamethonium administration, the available data do suggest that the concurrent administration of the two drugs not only enables greater and more prolonged reduction of blood pressure than does hexamethonium alone, but may also result in less untoward effects following comparable reduction in blood pressure. They also indicate that it may be desirable to begin the administration of hydrazinophthalazine before that of hexamethonium.

The goal in therapy of hypertensive patients is of course to lower the blood pressure without seriously reducing blood flow to the vital organs. This necessitates careful adjustment of drug dose to prevent rapid or excessive fall in blood pressure, both recumbent and erect, especially in patients with reduced serum sodium concentration or marked encephalopathy. In patients with renal insufficiency or malignant hypertension frequent determinations of the concentration of nonprotein nitrogen in the blood must be carried out, particularly during the initial period of blood pressure reduction. The presence of evidence of coronary insufficiency or of recent cerebral thrombosis has been considered to be a contraindication to attempted reduction in blood pressure. In view of the hazards that are involved, and the lack of information concerning the long term effects on the course of the disease, it would appear reasonable at this time not to administer these drugs routinely to patients with mild or asymptomatic hypertension, but to reserve them for patients in whom there are strong indications for lowering the blood pressure, such as hypertensive crises and encephalopathy, severe retinopathy, left heart failure, and subarachnoid hemorrhage. It would appear to be safer to aim for a reduction in blood pressure to intermediate than to normal levels, particularly in patients with malignant hypertension and in those who are ambulatory. It seems likely that other autonomic blocking drugs, or combinations of drugs, will be introduced which will prove to be even more satisfactory agents for reduction of blood pressure without impairment of blood flow.

Summary

1. Hexamethonium and pentamethonium produced comparable reduction in the blood pressure of hypertensive patients, following intravenous or oral administration. The reduction in pressure was greatest in the patients with malignant hypertension who had low serum concentration of sodium or severe encephalopathy. The response to methonium was increased by sodium depletion and by sympathectomy, and decreased by sodium restitution.

2. The repeated oral administration of hexamethonium or hydrazinophthalazine resulted in a reduction in the blood pressure of most hypertensive patients to levels intermediate between the original and normo-
tensive levels, and a slight reduction in the remainder. The development of tolerance necessitated increasing doses. Concurrent administration of the two drugs resulted in an additive effect on the blood pressure of most patients, with slower development of tolerance and less marked postural hypotension than following hexamethonium alone. It was possible to maintain the blood pressure of most patients with benign or malignant hypertension at intermediate levels for a period of several months. This resulted in improvement in many patients in signs and symptoms attributable to encephalopathy, and, to a lesser degree, to left ventricular decompensation and retinopathy. Improvement in the electrocardiogram occurred in a minority of patients.

3. Harmful effects of reduction in blood pressure occurred mainly in patients with malignant hypertension, and consisted of evidence of myocardial ischemia in four patients, of retinal ischemia in two, and renal insufficiency which progressed to terminal uremia in four. The latter occurred following hexamethonium administration, but was not observed in a smaller group of patients following concurrent administration of hexamethonium and hydrazinophthalazine. Some patients developed reduction in the hematocrit, which was attributable to hemodilution, following reduction in the blood pressure. An increase in extracellular fluid volume was measured in two patients.

4. The side effects of hexamethonium were minor, consisting of other evidences of autonomic blocking action, and, in a few patients, drowsiness and weakness. The side effects of hydrazinophthalazine consisted of headache, conjunctivitis, coryza, and, in a few patients, hiccups or fever.

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SUMARIO ESPAÑOL

Hexamethonium y pentamethonium produjeron una reducción mayor en la presión arterial en pacientes con hipertensión maligna que tenían una concentración del suero sódico baja o una encefalopatía que en aquellos con hipertensión benigna. Administración concurrente de hydrazinophthalazine resultó en un efecto aditivo en la presión arterial de la mayoría de los pacientes, con menor desarrollo de tolerancia y menor hipotensión postural. En muchos de los pacientes hubo signos y síntomas de mejoría atributables a la hipertensión. Efectos nocivos de la reducción en presión arterial ocurrieron principalmente en los pacientes con hipertensión maligna y consistieron en insuficiencia renal y evidencia de isquemia del miocardio y retinal.

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Further Observations on the Effects of Autonomic Blocking Agents in Patients with Hypertension: I. General Systemic Effects of Hexamethonium, Pentamethonium, and Hydrazinophthalazine
DAVID GROB, HERBERT G. LANGFORD and BARBARA ZIEGLER

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