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

II. Hemodynamic, Ballistocardiographic and Electrocardiographic Effects of Hexamethonium and Pentamethonium

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Moderate reduction in blood pressure by intravenous hexamethonium or pentamethonium was accompanied by a decrease in stroke volume, cardiac output, and left ventricular work, and no change or an increase in peripheral resistance. Renal blood flow, filtration rate, and potassium clearance fell promptly, but returned to the original levels within one to two hours despite continued reduction in blood pressure. Sodium clearance and urine flow were reduced to a greater extent and returned more slowly. Oral hexamethonium produced some reduction in renal blood flow, and improvement in the ballistocardiogram. Oral hydrazinophthalazine diminished the effect of hexamethonium on renal blood flow.

The ganglionic blocking agents, hexamethonium and pentamethonium [bis-trimethylammonium hexane (C₆) and pentane (C₅)], have been administered to hypertensive patients orally and parenterally in an effort to reduce the blood pressure,1-4 and to normotensive patients in order to increase blood flow to the extremities of patients with peripheral vascular disease1,5 and to produce postural hypotension and reduction of hemorrhage during certain operative procedures.6 The effects of hexamethonium and pentamethonium have been very similar.4 The studies to be reported were undertaken in an effort to determine the effect of reduction in the blood pressure, both recumbent and erect, by these compounds on the cardiac output, ventricular work, ballistocardiogram, electrocardiogram, and renal blood flow and function. Since 1-hydrazinophthalazine (Apresoline), a compound which has been reported to be a renal vasodilator,7 has an additive effect to that of hexamethonium on the blood pressure of hypertensive patients and is frequently administered orally concurrently with hexamethonium,2,4,8 the influence of this compound on the renal and ballistocardiographic effects of hexamethonium was also investigated.

Methods

The hypertensive patients who were studied varied in age from 18 to 64 (average 42) years. The patients who are classified as malignant hypertensives are those who had marked and sustained elevation of blood pressure, and some degree of renal insufficiency, papilledema, and encephalopathy.

All observations were preceded by a period of at least one week of bed rest in the hospital. Hexamethonium and pentamethonium dichloride 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 100 mg. had been administered. The amount injected varied from 4 to 100 mg. (average 52 mg., or 0.74 mg. per kilogram).
Hexamethonium dichloride and hydrazinophthalazine were administered orally at four- to six-hour intervals.4

Cardiac output (liters per minute) was determined by measurement of oxygen uptake and arteriovenous oxygen difference (Fick), employing the cardiac catheter for obtaining mixed venous blood. During cardiac output determinations arterial blood samples were obtained, and systemic blood pressure recorded by a strain gauge and Hamilton manometer, from an indwelling cannula in the brachial artery. In a small number of patients right auricular, right ventricular, pulmonary artery, and pulmonary capillary pressures were recorded from the cardiac catheter,9 and coronary sinus blood was obtained for estimation of coronary blood flow.10 Total peripheral resistance was calculated from the mean blood pressure (mm. Hg.) divided by the cardiac index (liters per minute per square meter of body surface), and ventricular work (kilogram meters per minute per square meter of body surface) was calculated from the product of the mean blood pressure and cardiac index, according to the formula of Starling.11

Renal blood flow was determined by clearance of para-aminophippuric acid,12 glomerular filtration rate by clearance of inulin,12,13 and sodium and potassium concentration in plasma and urine by flame photometry. Water loading was at a constant rate during the clearance procedures. The effect on renal blood flow and function of sitting, with the legs dangling over the sides of the bed, and of standing were determined before and after drug administration. Changes in posture were always active, rather than passive. The blood pressure was determined at frequent intervals by auscultation.

Head-foot and vector ballistocardiograms were recorded with a high-frequency bed, with simultaneous recording of electrocardiogram (lead II) and pneumogram.14 Measurements were made of wave amplitudes and time intervals in the ballistocardiograms, which were classified as “normal,” “borderline,” or “abnormal” on the basis of wave form.15 Electrocardiograms were recorded with a Sanborn Viso-Cardiette, and always included the standard limb, unipolar limb, and two unipolar precordial leads. The records were classified as “normal,” “borderline,” or “abnormal” on the basis of generally accepted criteria.

Results

Hemodynamic Effects

Effect of Intravenous Hexamethonium and Pentamethonium on Stroke Volume, Cardiac Output, Left Ventricular Work, and Peripheral Resistance (fig. 1). The amounts of methonium compound that were administered produced a slight reduction in systemic blood pressure in one patient, a moderate reduction in two, and a marked reduction in two. In the patient (F.M.) who had only a slight (10 per cent) reduction in mean pressure, which was still markedly elevated, there was an increase in stroke volume and cardiac output (by 50 per cent) and in left ventricular work (by 37 per cent), and a decrease in peripheral resistance (by 40 per cent). The cardiac rate was virtually unchanged. In contrast, in the four patients whose blood pressure fell to or near normo-
and left ventricular work was most marked in the two patients who had the most marked fall in blood pressure, to low normal levels, and particularly in the patient (L.M.) who had an unexplained, unusually high cardiac output and low peripheral resistance prior to hexamethonium administration. The latter patient also had the most striking increase in peripheral resistance following hexamethonium.

Forty-five minutes after the administration of pentamethonium to patient W.S. and 30 minutes after the initial cardiac output determination, the diastolic pressure had returned to the original level, and the systolic to a level intermediate between the original and postinjection pressures. The initial cardiovascular acceleration had diminished. The stroke volume, cardiac output, and left ventricular work continued to be moderately decreased, and the peripheral resistance slightly increased.

Effect of Standing. This was studied in two patients before and after pentamethonium administration. Prior to pentamethonium, standing resulted in a slight reduction in systolic pressure, a very slight increase in diastolic pressure, a slight increase in cardiac rate, a slight reduction in stroke volume (by 6 and 23 per cent), cardiac output (by 10 and 4 per cent), and left ventricular work (by 13 and 9 per cent), and a slight increase in peripheral resistance (by 12 and 3 per cent). Following pentamethonium, standing resulted in a moderate to marked reduction in systemic pressure (by 23 and 44 per cent of the control mean pressure), a marked reduction in stroke volume (by 61 and 67 per cent of control), cardiac output (by 46 and 57 per cent of control), and left ventricular work (by 74 and 51 per cent of control). The peripheral resistance increased (by 40 per cent of control) in the patient whose recumbent peripheral resistance had fallen following pentamethonium, and was unchanged in the patient whose peripheral resistance had increased following pentamethonium, remaining 32 per cent above the control value.

Effect on Right Auricular Pressure. This was measured in one patient (W.S.). The pressure was found to be 4/3 mm. Hg (recumbent) and 3/2 (erect) prior to pentamethonium and 2/0 (recumbent) and 13/11 mm. Hg (erect) following pentamethonium.

Effect on Coronary Blood Flow. This was estimated in two patients. In patient L.M., who had a marked reduction in cardiac output following hexamethonium, the recumbent coronary blood flow decreased only slightly, from 61 to 52 cc. per minute per square meter, while the calculated coronary resistance decreased from 2 to 1.7 mm. Hg per minute per square meter of surface area. In patient L.S., who had a moderate reduction in cardiac output following hexamethonium, the recumbent coronary blood flow was unchanged at 85 cc. per minute per square meter while the calculated coronary resistance decreased from 1.5 to 0.9 mm. Hg per liter per minute per square meter of body surface.

Effect on Pulmonary Circulation. This was measured in one patient (H.M.). Following moderate reduction in systemic arterial pressure by hexamethonium (by 13 per cent mean pressure) there was a moderate reduction in stroke volume (by 25 per cent), in cardiac output (by 21 per cent), and in left ventricular work (by 33 per cent). There was a slight increase in systemic resistance (by 11 per cent). Pulmonary artery and capillary pressure were unchanged (6.6 and 4.2 mm. Hg mean pressure). Pulmonary resistance increased (by 29 per cent), while right ventricular work decreased (by 19 per cent).

Effect on Renal Blood Flow and Function (Tables 1* and 2)

This was studied in four patients with benign hypertension and in one patient (R.C.) with early malignant hypertension. Two of the

* At the request of the Editor, table 1 is being omitted. This table will be furnished on request. The title of table 1 is, "Effect on blood pressure, cardiac rate, renal plasma flow, glomerular filtration rate, filtration fraction, potassium and sodium clearance, and urine flow of sitting or standing, intravenous and oral administration of hexamethonium, oral administration of hydrazinophthalazine, intravenous and oral administration of hexamethonium following hydrazinophthalazine, and sitting or standing following these drugs, in four patients with benign hypertension and one with early malignant hypertension."
former patients had normal renal blood flow and glomerular filtration rate, while the other three patients had moderately reduced renal blood flow and slightly to moderately reduced glomerular filtration. The concentration of hexamethonium on five occasions to four patients in doses sufficient to lower the blood pressure to normal or intermediate levels, by an average reduction in mean pressure of 25 per cent, resulted in prompt reduction in renal blood flow, glomerular filtration rate, and potassium clearance by an average of 59, 60, and 63 per cent, and in sodium clearance and urine flow by an average of 83 per cent. The filtration fraction was not changed. The cardiac rate increased slightly, by an average of 4 per cent. The renal blood flow returned to the

**FIG. 2.** Effect of intravenous hexamethonium on blood pressure (recumbent), renal plasma flow, glomerular filtration rate, potassium and sodium clearance, and urine flow of five hypertensive patients (D. P., 42 yrs., male, body surface area 1.92 M.², 100 mg. hexamethonium intravenously at rate of 3 mg. per minute (first experiment), at 15 mg. per minute (second experiment), and at 3 mg. per minute on nineteenth day of oral administration of hexamethonium, 7 Gm. four times daily (last experiment); S. L., 35 yrs., male, 2.05 M.², 75 mg.; E. P., 50 yrs., male, 1.80 M.², 18 mg.; R. C., 23 yrs., female, 1.50 M.², 80 mg.; and O. F., 26 yrs., female, 1.80 M.², 50 mg.). On the left is recorded the effect of moderate reduction in blood pressure, and on the right the effect of slight reduction. The average duration of each recorded period was 50 minutes.

blood nonprotein nitrogen was normal in the benign hypertensives at all times, while in the malignant hypertensive it was normal prior to hexamethonium administration, and increased during drug administration.

**Effect of Intravenous Hexamethonium (Figs. 2 and 3).** The intravenous administration of hexamethonium on blood pressure (recumbent), renal plasma flow, glomerular filtration rate, potassium and sodium clearance, and urine flow of five hypertensive patients (D. P., 42 yrs., male, body surface area 1.92 M.², 100 mg. hexamethonium intravenously at rate of 3 mg. per minute (first experiment), at 15 mg. per minute (second experiment), and at 3 mg. per minute on nineteenth day of oral administration of hexamethonium, 7 Gm. four times daily (last experiment); S. L., 35 yrs., male, 2.05 M.², 75 mg.; E. P., 50 yrs., male, 1.80 M.², 18 mg.; R. C., 23 yrs., female, 1.50 M.², 80 mg.; and O. F., 26 yrs., female, 1.80 M.², 50 mg.). On the left is recorded the effect of moderate reduction in blood pressure, and on the right the effect of slight reduction. The average duration of each recorded period was 50 minutes.

original levels over a period of 60 to 90 minutes after hexamethonium administration, even though the blood pressure increased but slightly during this time. The glomerular filtration rate returned a little more slowly than did the renal blood flow, and was not yet back to the original level when the renal blood flow had been restored. At that time there was a slight decrease in the filtration fraction (by an average of 5 per cent). The potassium clearance returned at approximately the same rate as did the glomerular filtration rate, while sodium clearance and urine flow were restored more slowly. Two hours after cessation of the injec-
<table>
<thead>
<tr>
<th>Observation</th>
<th>No. of Pts.</th>
<th>B.P. (mean)</th>
<th>Card. Rate</th>
<th>R F</th>
<th>G F R</th>
<th>F F</th>
<th>C K</th>
<th>U F</th>
<th>% Change</th>
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<tr>
<td></td>
<td></td>
<td>Range Avg</td>
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<td>Effect of I.V. Cₖ</td>
<td>5*</td>
<td>16 - 32 - 25</td>
<td>11 + 41 - 4</td>
<td>43 - 75</td>
<td>50 - 40 - 74</td>
<td>-9 + 6 - 2</td>
<td>-52 - 82 - 63</td>
<td>-73 - 98 - 82</td>
<td>-63 - 96 - 84</td>
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<td>Mod. fall in B.P.</td>
<td>2</td>
<td>-7 - 14 - 10</td>
<td>+3 + 34 - 18</td>
<td>-16 - 1 - 5</td>
<td>-3 - 1 + 9 + 4</td>
<td>-10 - 36 - 23</td>
<td>-50 - 71 - 65</td>
<td>-55 - 87 - 71</td>
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<td>Slight fall in B.P.</td>
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<td></td>
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<td></td>
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<tr>
<td>Sl. to Mod. fall in B.P.</td>
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<td>-22</td>
<td>+66</td>
<td>-88</td>
<td>-93</td>
<td>-80</td>
<td>-81</td>
<td>-73</td>
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<td>Mod. fall in B.P. &amp; progression of renal dis.</td>
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<td>-8</td>
<td>+2</td>
<td>+4</td>
<td>0</td>
<td>+37</td>
<td>+15</td>
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<td>-17</td>
<td>+8 + 60 + 34 + 66 - 60</td>
<td>-64 - 70 - 67</td>
<td>+4 - 7 + 2 - 69</td>
<td>78</td>
<td>-74</td>
<td>-70</td>
<td>-50 - 65</td>
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<tr>
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<td>+56</td>
<td>-45</td>
<td>-31</td>
<td>+22</td>
<td>-4</td>
<td>-61</td>
<td>-38</td>
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<td>+52</td>
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<td>-40</td>
<td>-81</td>
<td>-97</td>
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</table>

* Five observations in four patients.
† Four observations in three patients.
tion the sodium clearance and urine flow were still depressed by an average of 70 per cent. The rates of restoration of sodium clearance and urine flow varied from patient to patient, and were usually, but not always, parallel. In one patient the sodium clearance returned to the original level three hours after cessation of hexamethonium, at which time the urine flow was still depressed.

The degree of reduction of renal blood flow and function varied with the degree and rate of reduction of blood pressure. Patient D.P. received 100 mg. of hexamethonium intravenously on three occasions. Rapid injection, which produced a more rapid and slightly more marked fall in blood pressure than did slow injection, resulted in slightly greater reduction in renal blood flow and glomerular filtration rate. Injection of the drug at a time when the patient had become tolerant to orally administered hexamethonium resulted in only a very slight fall in blood pressure, a slight reduction in renal blood flow and glomerular filtration, and a moderate reduction in potassium and sodium clearance and urine flow. Similar changes occurred in another patient (O.F.), who had mild hypertension and a slight fall in blood pressure after intravenous hexamethonium. In each instance the potassium clearance was reduced to about the same degree and for the same time as the renal blood flow and glomerular filtration rate, while the sodium clearance and urine flow were reduced to a greater degree and over a more prolonged period. The effect of intravenous hexamethonium on renal blood flow and function was the same in patients with normal and with reduced renal blood flow.

Effect of Oral Hexamethonium (Fig. 4). In two patients (S.L. and O.F.) who had a moderate (14 per cent) reduction in mean blood pressure following oral administration of hexamethonium for 14 and 27 days, there was some reduction in renal blood flow (by 32 and 10 per cent). In another patient (D.P.), whose blood pressure did not fall, there was no change. The glomerular filtration rate was slightly reduced (by 11 per cent) in one patient (S.L.). The filtration fraction was slightly increased (by 22 and 11 per cent) in the two patients whose renal blood flow was reduced. The potassium and sodium clearance and urine flow were not significantly decreased.

In the patient with early malignant hypertension (R.C.) reduction in blood pressure to normotensive levels was accompanied by marked reduction in glomerular filtration rate, filtration fraction, potassium and sodium clearance, and urine flow, and a moderate increase in renal blood flow (tables 1* and 2). The concentration of nonprotein nitrogen in the blood increased from 33 to 64 mg. per 100 cc. Hexamethonium administration was discontinued, following which the blood pressure returned to the original hypertensive level. In spite of this, nitrogen retention progressed and the patient died in uremia 15 days later. Postmortem examination of the kidneys revealed severe arteriolosclerosis of the small cortical arteries and scattered necrotic intraglomerular arterioles.

Effect of Intravenous and Oral Hexamethonium on Postural Changes in Renal Blood Flow and Function (Figs. 3 and 4). Prior to hexamethonium administration, sitting for 30 minutes resulted, in four observations on three patients, in reduction in renal blood flow by an average of 30 per cent, in glomerular filtration rate by an average of 26 per cent, and in potassium and sodium clearance and urine flow by an average of 33 per cent. The filtration fraction increased by 7 per cent in three of the observations. Standing for the same period of time led to reduced renal blood flow, glomerular filtration, and clearances and urine flow by an average of 54, 45, and 51 per cent, and increase in filtration fraction by an average of 20 per cent. Sitting or standing prior to hexamethonium resulted in a very slight reduction in systolic pressure and a very slight increase in diastolic pressure. When the recumbent position was resumed for a period of 40 minutes, following sitting or standing, the renal blood flow, filtration rate, potassium and sodium clearances and urine flow returned to the original levels.

Following intravenous or oral hexamethonium administration, sitting or standing resulted in moderate or marked reduction in

* See footnote p. 354.
blood pressure to, near, or below normotensive levels. This was accompanied by reduction in renal blood flow, filtration rate, and potassium clearance to levels that were slightly lower than had occurred on sitting or standing prior to hexamethonium, and of sodium clearance and urine flow to levels that were moderately lower. In 10 observations in five patients, sitting and standing after intravenous or oral hexamethonium resulted in reduction in mean blood pressure by an average of 30 per cent (sitting) and 32 per cent (standing) of the control recumbent values, in renal blood flow by 55 and 60 per cent, in glomerular filtration rate by 48 and 59 per cent, in potassium clearance by 63 and 42 per cent, in sodium clearance by 71 and 82 per cent, and in urine flow by 85 and 88 per cent. The sodium clearance and urine flow were reduced to a greater degree than the renal plasma flow and glomerular filtration rate, in contrast to the changes that occurred on sitting or standing prior to hexamethonium. In addition, when the recumbent position was resumed the sodium clearance and urine flow did not return to the recumbent levels as rapidly as prior to hexamethonium. The filtration fraction did not change significantly on standing, in contrast to the increase that occurred prior to hexamethonium. On the other hand, the filtration fraction increased on sitting to a greater extent than prior to hexamethonium. The slight to moderate cardio-acceleration that occurred on sitting or standing was approximately the same before and after hexamethonium. The level to which renal blood flow and function fell during postural hypotension was approximately the same after intravenous and oral hexamethonium, and was the same when the recumbent blood pressure was elevated as when it had been reduced to normotensive levels by hexamethonium.

Effect of Oral Hydrazinophthalazine. The oral administration of 600 mg. of hydrazinophthalazine daily to two patients for five and eight days resulted in a very slight (8 per cent) increase in renal blood flow (table 1, d-g*). Glomerular filtration rate increased by 26 per cent in one patient, and decreased by 49 per cent in the other patient, whose filtration fraction also decreased. The potassium and sodium clearance and urine flow were not significantly changed. The mean systemic pressure was reduced by 12 per cent in one patient, and was not altered in the other.

Hydrazinophthalazine administration had no significant effect on the slight reduction in renal blood flow and glomerular filtration rate that occurred following oral hexamethonium, and no effect on the reduction in renal blood flow and function that occurred on sitting

* See footnote p. 354.
or standing, either before or after the oral or intravenous administration of hexamethonium. It did appear to diminish to some extent the degree of reduction in renal blood flow, and to a lesser extent in glomerular filtration rate, that occurred immediately after the intravenous administration of hexamethonium (table 2). Whereas there was no alteration in the filtration fraction immediately after intravenous hexamethonium, there was a 20 per cent decrease when hexamethonium was administered following hydrazinophthalazine. There was no change, however, in the reduction in potassium and sodium clearance, and in urine flow, that occurred following intravenous hexamethonium. Although the amount of hexamethonium injected was less in one patient during hydrazinophthalazine administration, the reduction in blood pressure was actually slightly greater.

Effect on the Ballistocardiogram

Observations were carried out in 19 hypertensive patients (13 benign and 6 malignant), whose ages ranged from 18 to 64 (average 42) years. The ballistocardiogram was normal in only one patient, who was the youngest in the group (18 years) and who had the shortest known duration of hypertension (nine months). Sixteen patients had abnormal ballistocardiograms, and in two patients the records were considered to be borderline. In 11 of the abnormal records two characteristic alterations were noted. There were relatively deep, broad, slurred or doubled K waves, and small and distorted or absent I and J waves in the conventional head-foot record. The I and J waves were nearly normal in one of the vector records, suggesting rotation of the IJ axis. In some patients the L wave was unusually prominent. Aside from these alterations there was considerable variation in form in the abnormal ballistocardiograms. In the other five abnormal records the form was so abnormal that identification of specific waves was impossible. In seven patients the amplitude was abnormally low.

Effect of Intravenous Methonium (Tables 3* and 5). Twelve patients were administered hexamethonium and two pentamethonium, in doses of from 4 to 100 mg. (average 51 mg.). These doses lowered the blood pressure to

![Fig. 5. Improvement in ballistocardiogram of a patient with early malignant hypertension (R. C., age 23) following reduction in blood pressure by intravenous pentamethonium and by oral hexamethonium. (A) Control. Ballistocardiogram is low in amplitude and grossly abnormal in form, with only an occasional normal complex. (B) After intravenous pentamethonium. Amplitude of ballistocardiogram is increased and complexes are more clearly defined. (C) During oral hexamethonium. Further increase in amplitude and improvement in form. Although the L waves are prominent, the record is within normal limits.

(In this figure, and in figures 6-8, the upper tracing on each record is the pneumogram (Resp.), the middle tracing is the ballistocardiogram (BCG), and the lower tracing is the electrocardiogram (EKG—lead II). Vertical time lines are 0.1 second apart. The bracketed vertical line (C) in the upper right hand corner of the top record represents 1 cm. calibration, and applies to all records in each figure.)

normal in five patients, to levels slightly above normal in four, and to levels intermediate between the original hypertensive and

* At the request of the Editor, table 3 is being omitted. This table will be furnished on request. The title of table 3 is, "Effect of intravenous hexamethonium and pentamethonium on the electrocardiogram and the ballistocardiogram."
normal in five. One patient received hexamethonium on two occasions, once in sufficient amount to lower the blood pressure to low normal, and once to an intermediate level. The average blood pressure of the 14 patients studied was 222/131, and following methoninum 149/100. There was no alteration in the average cardiac rate.

Following methoninum administration there was improvement in the ballistocardiogram in six patients (figs. 5 and 6), and in three of these the record became normal. Improvement in form often consisted of diminution in the abnormally deep K wave, and increase in the abnormally low I and J waves (fig. 6). In three patients the records became more abnormal, with almost complete disappearance of the systolic complexes (fig. 7), and in five patients there was no change. In six patients there was a decrease in amplitude of the ballistocardiogram, accompanied in two by improvement in form, in three by no change in form, and in one by greater abnormalities in form. In one patient there was a striking increase in amplitude, accompanied by improvement in form. In most patients there were changes in the timing of the ballistic systolic waves, consisting of an increase in the duration of the Q-I, Q-J, and Q-K intervals, by a mean of 0.03, 0.03, and 0.04 second, respectively.

The effect of methoninum injection on the ballistocardiogram could not be correlated with the precise degree of reduction in the blood pressure. Improvement occurred after reduction to, or near, normotensive levels in four patients, and to an intermediate level in two. The ballistocardiogram became more abnormal after reduction in pressure to near normal in one patient, and to an intermediate level in two. There was no change after reduction in pressure to normal in two patients, to near normal in two, and to intermediate levels in two. One patient did have improvement in the ballistocardiogram after reduction in pressure to 100/70 mm. Hg (fig. 6), and this improvement was not maintained when the blood pressure rose to an intermediate level. There was likewise no correlation with the level of systolic or diastolic pressure prior to drug

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Fig. 6. Slight improvement in ballistocardiogram of a patient with malignant hypertension (H. B., age 37) following reduction in blood pressure by intravenous hexamethonium, and more marked, though temporary, improvement in ballistocardiogram, with improvement in electrocardiogram, following lesser reduction in blood pressure by oral hexamethonium. (A) Control. Ballistocardiogram is abnormal, showing no definite I waves, and unusually deep K and prominent L waves. Electrocardiogram shows left bundle branch block. (B) After intravenous hexamethonium, there has been reduction in amplitude of K and L waves. The I waves are distorted and variable, but are deeper than in the control record. (C) After 15 days of oral hexamethonium and hydrazinophthalazine, ballistocardiogram is markedly improved and is now within normal limits, even though the blood pressure is considerably above normal, though lower than the original level. Electrocardiogram reveals that the bundle branch block has been replaced by left ventricular “strain” pattern. (D) After 22 days of the same medication the ballistocardiogram has reverted to the abnormal form seen in the control record, despite further slight reduction in the blood pressure. The tracing again shows small or absent I waves and deep K waves. The electrocardiogram has not reverted to the control form, indicating that bundle branch block was not responsible for the ballistocardiographic abnormality of the control record, and that disappearance of the conduction defect was not responsible for ballistocardiographic improvement (C).
administration, or with the benign or malignant characterization of the hypertension. All four patients with malignant hypertension (ages 19 to 45, mean 30 years) had improvement in the ballistocardiogram after methonium administration. There did appear to be some variation in degree of ballistic improvement with the age of the patient, and perhaps with the duration of the hypertension. If the 18 year old patient whose control ballistocardiogram was normal and who had no change after methonium is excluded, the average age of the patients whose ballistocardiograms improved was 34 years (range 19 to 47 years), of those in whom there was no change 48 years (range 46 to 50 years), and of those whose ballistocardiograms became worse 52 years (range 47 to 56 years).

Following Oral Administration (Tables 4* and 5). Seven patients were administered 0.5 to 6 (mean 2.7) Gm. of hexamethonium per day for 9 to 21 (mean 16) days, and six patients were given similar doses of hexamethonium together with 100 to 600 mg. (mean 310) of hydrazinophthalazine per day, five for 15 to 22 (mean 19) days and one for 252 days. In three patients the ballistocardiogram was recorded during both hexamethonium and combined drug administration. Five patients had been studied previously following the intravenous injection of hexamethonium. At the time ballistocardiograms were obtained during oral administration of hexamethonium the blood pressure had been reduced to, or near, normal in three patients, to intermediate levels in three, and only slightly in one. The average blood pressure fell from 211/131 to 162/97. At the time the ballistocardiograms were obtained during combined drug administration the blood pressure had fallen to near normal in two patients, and to intermediate levels in four. The average blood pressure fell from 226/142 to 176/103. There was no significant change in cardiac rate. During the first week of drug administration the blood pressure was, in most patients, slightly to moderately lower than at the time ballistocardiograms were obtained.

*At the request of the Editor, table 4 is being omitted. This table will be furnished on request. The title of table 4 is, "Effect of Oral Hexamethonium and Hexamethonium plus Hydrazinophthalazine on the Electrocardiogram and the Ballistocardiogram."
to some extent with the form of the control record. Abnormalities of the K wave tended to decrease or disappear (figs. 6 and 8). I and J waves generally became larger and more clearly defined (figs. 5, 6, and 8), the mean IJ amplitude increasing by 5 mm. or more in 7 of the 10 patients. Prominent H waves and abnormal diastolic waves, when present, tended to diminish. There was an increase in amplitude, at times marked, in six patients. There

The degree of ballistic improvement was greater in the younger patients, and was least in the two patients who were over 50 years of age. The degree of improvement could not be related to the degree of reduction in blood pressure, or to the benign or malignant characterization of the hypertension. Both slight and marked improvement occurred following reduction in blood pressure to normal and following reduction to intermediate levels.

**Table 5.—Summary of the Effect of Hexamethonium (or Pentamethonium) on the Electrocardiogram and Ballistocardiogram**

<table>
<thead>
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<th>Control</th>
<th>After I.V.C.</th>
<th>Control</th>
<th>After I.V.C.</th>
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<tbody>
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<td></td>
<td>Improved</td>
<td>Worse</td>
<td>Unchanged</td>
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<td>3</td>
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<td>1</td>
</tr>
<tr>
<td>A*</td>
<td>10</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

2. Effect of prolonged oral administration (with or without hydrazinophthalazine):

<table>
<thead>
<tr>
<th>Control</th>
<th>On Oral C6</th>
<th>Control</th>
<th>On Oral C6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improved</td>
<td>Worse</td>
<td>Unchanged</td>
</tr>
<tr>
<td>N</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>A</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

*N = normal record, B = borderline, and A = abnormal.

was no significant change in the timing of the ballistic waves. The effect of combined drug administration was, in general, similar to the effect of hexamethonium alone.

Recordings were obtained on two or three occasions during drug administration in four patients. In one patient there was further improvement in the second and third records as the blood pressure was progressively lowered to near normal. In one patient slight improvement persisted, and in two patients the second record reverted toward the control, even though the blood pressure continued to be moderately reduced (fig. 6, C and D).

There were not sufficient observations to ascertain the relation of the degree of ballistic improvement to the duration of the reduction in blood pressure, or to the clinical course of the patient. All the patients whose ballistocardiogram became normal showed improvement in many of the signs and symptoms attributable to hypertension, including those attributable to left ventricular decompensation, concomitant with the reduction in blood pressure. However, the two oldest patients, who had only slight ballistic improvement, despite moderate to marked reduction in blood pressure, had comparable symptomatic im-
improvement. The degree of ballistic improvement could not be related to the rate of development of tolerance to the antihypertensive effect of the drugs. Improvement in the ballistocardiogram was more marked after prolonged oral than after acute intravenous administration of hexamethonium in four of the five patients who received the drug by both routes.

**Effect on the Electrocardiogram**

Electrocardiograms were recorded simultaneously with the ballistocardiogram. Of the 19 patients who were studied, 13 had abnormal electrocardiograms, four had tracings which were considered to be borderline, and two had normal records. In 12 of the abnormal electrocardiograms a left ventricular “strain” pattern was present, and in the other abnormal record there was left bundle branch block. In the four borderline electrocardiograms there were minor T-wave changes, and in three of the four, left axis deviation.

**Effect of Intravenous Methonium (Tables 3* and 5).** Following hexamethonium or pentamethonium there were minor changes in the electrocardiogram in seven patients, and no change in seven. In four patients there was some improvement in the electrocardiogram, consisting of S-T segment and T-wave changes and, in only one of these, some shift of the QRS axis toward normal. In no instance, however, did the electrocardiogram become normal. In three patients the pre-existing S-T segment and T-wave changes were accentuated.

**Effect of Oral Hexamethonium (Tables 4† and 5).** There was moderate improvement in the electrocardiogram of two patients, consisting of disappearance of left ventricular “strain” pattern in one (fig. 8) and replacement of left bundle branch block by left ventricular strain in the other (fig. 6). In four patients there was minor improvement, consisting mainly of S-T segment and T-wave changes, and in four patients there was no change. None of the abnormal electrocardiograms became normal, but one record which had been classified as borderline became normal, and one abnormal record became borderline. Changes in QRS axis were insignificant. The effect of hexamethonium plus hydrazinophthalazine appeared to be the same as of hexamethonium alone. The degree of improvement in the electrocardiogram was somewhat greater after prolonged oral than after acute intravenous administration of hexa-

![Fig. 8. Improvement in ballistocardiogram and electrocardiogram of a patient with essential hypertension (G. Y., age 47) following reduction in blood pressure by oral hexamethonium. (A) Control ballistocardiogram, showing short I waves and an unusual late systolic-early diastolic pattern. There are deep K waves and very short L waves which never return to the base line. The M waves are deep, at times deeper than the K waves, and occasionally fuse with the K waves to form large, broad footward waves. The N waves are quite prominent and at times equal the J waves in height. (B) Control electrocardiogram, showing left ventricular “strain” pattern. (C) Ballistocardiogram during oral hexamethonium is normal. IJ amplitude has doubled and the unusual KLMN wave pattern has disappeared. (D) Electrocardiogram during oral hexamethonium shows disappearance of left ventricular “strain” pattern. T waves are low in leads I and V₆.](http://circ.ahajournals.org/)

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* See footnote p. 359.
† See footnote p. 361.
nant versus benign character of the hypertension. There was insufficient data to establish any correlation with the duration of reduction in blood pressure or with the clinical course, although it is of interest that the only patient who had disappearance of a left ventricular strain pattern had the longest period of reduction in blood pressure. Although the changes in the ballistocardiogram that occurred following methonium were much more striking than the changes in the electrocardiogram, the two usually changed in the same direction. In only two instances did one record become worse when the other improved.

**DISCUSSION**

**Hemodynamic Effects**

The basis of hypertension is increased systemic peripheral resistance, perhaps due, in part, to increased sympathetic vasoconstrictor tone. In uncomplicated hypertension the cardiac output is usually normal, but because of the increased systemic blood pressure the blood flow to the heart, brain, and extremities is usually near normal until fixed vascular changes ensue, while that to the kidneys is usually slightly to moderately reduced. In the management of hypertensive disease the goal is reduction of blood pressure without serious impairment of blood flow to the vital organs. The reduction in blood pressure produced by hexamethonium or pentamethonium is believed to be due to reduction in sympathetic vasoconstrictor tone resulting from inhibition of ganglionic conduction, though the location of the areas where vasodilatation occurs, other than the skin, is not known. It is possible that the splanchnic bed may be important in this regard. Following slight reduction in blood pressure by intravenous methonium, the increased cardiac output that occurred is compatible with the maintenance of blood flow to most areas. Following moderate or marked reduction in blood pressure, on the other hand, the reduction in cardiac output that occurred is compatible with reduction in blood flow to some areas. This would be expected to be most marked wherever fixed vascular changes are present. Clinical evidence suggestive of reduction in renal, coronary, cerebral, and retinal blood flow following reduction in the blood pressure by hexamethonium has occurred in some patients and has been more frequent and more marked in patients with malignant hypertension than in those with benign hypertension.

The reduction in cardiac output produced by methonium is most likely due to decreased venous return resulting from the pooling of blood in peripheral areas of vasodilation. The decrease in right auricular pressure that occurred is compatible with this, but may also have been due to decreased venomotor tone. A direct depressant effect of methonium on the heart cannot be entirely excluded, though such an effect has not been demonstrated. The lack of change, or increase in the calculated peripheral resistance reflects the greater reduction in cardiac output than in mean arterial pressure. Since the pulmonary artery and capillary pressures did not change, and the calculated pulmonary resistance increased, pooling of blood probably did not occur in the pulmonary circulation. Werko and his associates observed a reduction in cardiopulmonary blood volume in three hypertensive patients following reduction in blood pressure by hexamethonium, even though pulmonary artery and capillary pressures fell to some extent. The systemic peripheral resistance was reported to have decreased in these patients, and the cardiac output to have decreased in two of the three.

Since the estimated coronary blood flow was unchanged or only slightly reduced, and the calculated coronary resistance reduced following lowering of the blood pressure by hexamethonium, it would appear that the coronary vessels were under resting sympathetic tone, and that coronary vasodilatation occurred immediately after hexamethonium injection in the patients studied. Vasodilatation apparently does not always occur, since electrocardiographic changes compatible with reduced coronary blood flow occurred following reduction in blood pressure by hexamethonium in two patients with malignant hypertension, and fatal myocardial infarction, has been reported.

The postural hypotension which occurs as
a result of inhibition of reflexly mediated peripheral vasoconstriction by the ganglionic blocking action of methonium is associated with a marked reduction in stroke volume and cardiac output, and either no change or an increase in calculated peripheral resistance. The reduction in stroke volume and cardiac output are probably the result of decreased venous return following pooling of blood in the peripheral circulation. Whatever the cause, the reduction in cardiac output that occurs during postural hypotension would be expected to result in decreased blood flow to some areas. The frequent occurrence of syncope is, of course, a reflection of decreased cerebral blood flow. The need for study of the effect of hexamethonium-induced postural hypotension on blood flow to the vital organs is evident, particularly since the recommendation has been made that hypertensive patients receiving hexamethonium sleep in a semi-recumbent position to facilitate reduction of their blood pressure throughout 24 hours. The administration of hydrazinophthalazine usually produces some increase in cardiac rate, and intravenous administration has been reported to produce an increase in stroke volume and cardiac output. It is possible that the concurrent administration of sufficient hydrazinophthalazine may prove capable of reducing the depression of cardiac output that may follow hexamethonium.

The reduction in renal blood flow that occurred immediately following reduction in blood pressure by intravenous hexamethonium indicates that renal vasodilatation did not occur at that time, while the gradual recovery of renal blood flow, long before the blood pressure, points to the gradual occurrence of renal vasodilatation. Similar changes in renal blood flow were observed by Smith following spinal anesthesia, and were interpreted by him as indicating that the renal vascular tree is not under resting sympathetic vasoconstrictor tone, but is capable of autonomous regulation of tone.

The reduction in glomerular filtration rate and potassium clearance that occurred paralleled in general, and probably depended upon, the reduction in renal blood flow. The reduction in sodium clearance and urine flow, on the other hand, exceeded and was more prolonged than the reduction in renal blood flow and glomerular filtration rate. Following reduction in blood pressure, the latter changes are known to be accompanied by increased tubular reabsorption of sodium and water, but the relative roles of decreased filtration rate and blood flow, and of release of a circulating antinatriuretic and antidiuretic substance are not known.

In the patients with benign hypertension reduction in blood pressure by oral hexamethonium resulted in some reduction in renal blood flow and, to a lesser extent, in glomerular filtration rate, but no observed decrease in potassium or sodium clearance or in urine flow. However the occurrence of hemodilution and of increased extracellular fluid volume in some patients following reduction in blood pressure by oral hexamethonium suggests that sodium and water retention may occur. In the patient with malignant hypertension who was studied, reduction in blood pressure by oral hexamethonium was followed by marked reduction in glomerular filtration rate, filtration fraction, potassium and sodium clearance and urine flow, moderate increase in renal blood flow, and increased nitrogen retention which later progressed to uremia in spite of discontinuation of hexamethonium and return of hypertension. The reduction in blood pressure induced by hexamethonium in this patient was apparently accompanied by a rapid increase in renal damage, with irreversible changes. The functional alterations that were observed suggest that, at the time the studies were carried out, diversion of blood to extra-glomerular shunts may have occurred, but the relation of this to the ganglionic blocking effects of hexamethonium, or to the reduction in blood pressure and damage to glomerular arterioles (observed post mortem), is not clear.

The reduction in renal blood flow, glomerular filtration rate, potassium and sodium clearance and urine flow that occurred in the hypertensive patients on sitting or standing prior to drug administration was greater than that described in normal subjects. This was true of hypertensive patients with normal renal blood flow, as well as of those with reduced renal blood flow. The postural reduction in
renal blood flow is probably due to reflexly mediated renal vasoconstriction, since the cardiac output falls very slightly, if at all, on standing or sitting. The occurrence of more marked reduction in hypertensive patients than in normal subjects may reflect more marked peripheral vasoconstriction required to maintain the elevated blood pressure in the erect position. The increase in filtration fraction that occurs in both hypertensive and normal subjects on standing indicates that efferent vasoconstriction may be greater than afferent. The reduction in the various renal functions was equal to the reduction in renal blood flow, indicating that the latter was responsible. Following hexamethonium administration, sitting or standing resulted in only slightly greater reduction in renal blood flow, glomerular filtration and potassium clearance than had occurred prior to hexamethonium, in spite of the reduction in blood pressure and cardiac output. Since reflexly mediated vasoconstriction is inhibited by hexamethonium, the reduction in renal blood flow would appear to be due to the reduction in blood pressure and cardiac output. There was no change in the filtration fraction on standing following hexamethonium, but the filtration fraction did increase during sitting. The sodium clearance and urine flow fell to a greater degree on sitting or standing following hexamethonium than did the renal blood flow, filtration rate, and potassium clearance, and whereas the latter returned to the original levels when the patient resumed the recumbent position, the former, particularly the urine flow, remained depressed. The reduction in sodium clearance and urine flow would appear to be the result not only of reduction in glomerular filtration rate and renal blood flow, but also of some additional antidiuretic and antinatriuretic effect of reduction in the blood pressure.

Intravenously administered hydrazinophthalazine has been reported to increase stroke volume, cardiac output, and renal blood flow in many hypertensive patients. Oral administration to two patients, however, had little or no effect on renal blood flow or function, or on the effect of sitting or standing on renal blood flow and function either before or after intravenous or oral hexamethonium. It did appear to diminish the effect of intravenous hexamethonium on renal blood flow, and, to a lesser extent, on glomerular filtration rate. Whether this was mediated through alteration of the effect of hexamethonium on cardiac output, or through more rapid renal vasodilatation following reduction in blood pressure remains to be determined. The relation of this "protective" influence of hydrazinophthalazine to the much lower incidence of renal insufficiency observed during combined drug administration than during hexamethonium administration also remains to be determined. Hydrazinophthalazine did not diminish the marked reduction in sodium clearance and urine flow which followed intravenous hexamethonium. This suggests that the antinatriuretic and antidiuretic effect of reduction in blood pressure by hexamethonium may be due in part to the release of a circulating substance by some other organ than the kidney, since it was not entirely dependent on reduced renal blood flow.

**Ballistocardiographic and Electrocardiographic Effects**

The high incidence and nature of the ballistocardiographic abnormalities observed in the hypertensive patients studied are in accord with the findings of other observers. The cause of these abnormalities is not clear, though it is believed that the more advanced changes are due to inability of the heart to eject blood with normal force, and that the deep K wave and "late downstroke" patterns may be due to ejection of blood with maximum velocity much later in systole by the chronically overburdened hypertensive heart than by the normal heart. The relative importance of increased peripheral resistance and of other alterations in cardiovascular function in the development of abnormalities in ballistic form is not clear. While deep K and short I waves may occur following compression of the abdominal aorta, the production of a transient increase in general peripheral resistance and in blood pressure by the administration of pressor agents to normal subjects does not
result in abnormal ballistic form, though it may result in a change in amplitude.28,29

Improvement in the ballistocardiogram, presumably reflecting improvement in the ejection of blood by the heart, was more common and more striking after prolonged reduction in the blood pressure by oral hexamethonium or hexamethonium plus hydrazinophthalazine than after more acute reduction by intravenous hexamethonium. This was also true of the less striking improvement in the electrocardiogram. Worsening of the ballistocardiogram occurred only after intravenous administration of drug, and in the case of the electrocardiogram was more frequent after intravenous than oral administration. It is not clear whether these differences are due to the more rapid reduction in blood pressure after intravenous than after oral administration of drug, or to the more prolonged reduction in blood pressure during oral administration. However, it is of interest that worsening of the ballistocardiogram has been reported to occur immediately after sympathectomy and improvement several months later.25 Improvement in the ballistocardiogram has also been reported to have occurred in a few instances following reduction of blood pressure by an antipressor kidney extract,28 and in two patients following veratrum viride.29

There was usually an increase in the amplitude of the ballistocardiogram following oral hexamethonium, whereas a decrease in amplitude was more common after intravenous administration. The ballistic changes could not be correlated with the degree of reduction in blood pressure, and the abnormalities of ballistic form that were present precluded calculation of cardiac output from these tracings. There was, in addition, an increase in the average Q-I, Q-J, and Q-K intervals after intravenous but not after oral drug. It is possible that the delay in the systolic waves may reflect a decrease in pulse-wave velocity, although the intervals were not unusually short prior to hexamethonium.

The cause of the differences between the effects of intravenous and of prolonged oral administration is not known, but the occurrence of differences suggests that the hemodynamic effects of the drug may not be the same in each instance, and that it may not be possible to predict the effects of prolonged oral administration from those observed after intravenous injection.

The degree of ballistocardiographic improvement following reduction in blood pressure by hexamethonium was much greater in patients under 50 years of age than in those over 50. This difference may be due to the fact that the ballistocardiogram is frequently abnormal even in clinically normal persons over 50 years of age.15 Such factors as coronary artery disease, aortic atherosclerosis and minimal pulmonary emphysema may be responsible for ballistocardiographic changes, and may limit the degree of ballistic improvement following reduction in the blood pressure of older hypertensive subjects.

**Summary**

1. Slight reduction in blood pressure by intravenous hexamethonium or pentamethonium was accompanied by an increase in stroke volume, cardiac output, and left ventricular work, and a decrease in calculated peripheral resistance. Moderate or marked reduction in blood pressure was accompanied by a decrease in stroke volume, cardiac output, and left ventricular work, and either no change or an increase in peripheral resistance. When the patient stood up, there was a further reduction in blood pressure, stroke volume, cardiac output, and left ventricular work, and either no change or an increase in peripheral resistance. The right auricular pressure decreased following methonium while the patient was recumbent, but increased when the patient stood up. Coronary blood flow was unchanged or slightly reduced following methonium, while coronary resistance decreased. Pulmonary artery and capillary pressure was unchanged, while pulmonary resistance increased slightly.

2. Moderate reduction in blood pressure by intravenous hexamethonium was followed by prompt reduction in renal blood flow, glomerular filtration rate, and potassium clearance, and, to a greater extent, in sodium clearance and urine flow. The renal blood flow returned
to the original levels over a period of 60 to 90 minutes, even though the blood pressure increased but slightly. Glomerular filtration rate and potassium clearance increased a little more slowly, and sodium clearance and urine flow considerably more slowly. Reduction in blood pressure by oral hexamethonium was accompanied by some reduction in renal blood flow, and, to a lesser extent, in glomerular filtration rate. Sitting or standing following intravenous or oral hexamethonium resulted in reduction in renal blood flow, filtration rate, and potassium clearance to levels that were slightly lower than had occurred on sitting or standing prior to hexamethonium, and of sodium clearance and urine flow to levels that were moderately lower. The oral administration of hydrazinophthalazine resulted in only a very slight increase in renal blood flow, but it did appear to diminish the degree of reduction in renal blood flow that occurred following the intravenous administration of hexamethonium.

3. Following the intravenous administration of hexamethonium or pentamethonium there was improvement in the ballistocardiogram in 6 of 14 patients, and increased abnormality in three patients. There was slight improvement in the electrocardiogram in four patients, and increased abnormality in three. Following the oral administration of hexamethonium or of hexamethonium plus hydrazinophthalazine there was improvement in the ballistocardiogram in each of 10 patients, and an increase in amplitude in six of these. There was moderate improvement in the electrocardiogram in two patients, and minor improvement in four. The degree of ballistic improvement that occurred was greater in the younger patients.

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SUMARIO ESPAÑOL

Reducción moderada de la presión arterial con hexamethonium o pentamethonium intravenoso fué acompañada por un decremento en emisión sistólica, en producción total cardíaca y en trabajo del ventrículo izquierdo, y ningún cambio o un incremento en resistencia periférica. La circulación renal, promedio de filtración y depuración del potasio disminuyó prontamente, pero volvió a su nivel original en una o dos horas no obstante continua reducción en presión arterial. La depuración del sodio y producción de orina fueron reducidas más marcadamente y volvieron a su nivel original más lentamente. Hexamethonium oral produjo alguna reducción en circulación renal y mejoría en el balistocardiograma. Hydrazinophthalazine oral disminuyó el efecto del hexamethonium en la circulación renal.

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Further Observations on the Effects of Autonomic Blocking Agents in Patients with Hypertension: II. Hemodynamic, Ballistocardiographic and Electrocardiographic Effects of Hexamethonium and Pentamethonium

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