HEXAMETHONIUM—ITS EFFECT ON GLOMERULAR FILTRATION RATE, MAXIMAL TUBULAR FUNCTION, AND RENAL EXCRETION OF ELECTROLYTES[1]

By JOHN H. MOYER and LEWIS C. MILLS with the technical assistance of MISS C. POLK SMITH

(From the Departments of Medicine and Pharmacology, Baylor University College of Medicine, Houston, Texas)

(Submitted for publication September 10, 1952; accepted November 26, 1952)

Hexamethonium chloride is an autonomic ganglionic blocking drug which has been reported to be effective in reducing blood pressure (1–3). In patients with severe hypertensive vascular disease the brain and the heart appear to be benefited by a moderate reduction in blood pressure (2–5). However, since glomerular filtration is dependent upon systemic blood pressure, one might anticipate that renal excretory capacity may be affected adversely by this procedure, particularly if kidney disease is associated with the hypertension. For this reason, the following study was undertaken, in which renal functions were evaluated before and after reduction in blood pressure with hexamethonium.[2] The studies were carried out on control subjects with normal blood pressure and on patients with hypertension with and without renal damage as estimated by glomerular filtration rate.

METHODS

Observations on the effect of hexamethonium administered intravenously were made on 14 control subjects (six men and eight women) with normal blood pressure and on 22 patients (13 men and nine women) with hypertension. Maximal tubular function (TmPAH) before and after blood pressure reduction was determined on four of the normal subjects and on six of the patients with hypertension. Para-aminohippurate (PAH) at plasma levels of 60 to 90 mg. per 100 ml. of plasma was used for this measurement. The analytical method of Smith and his associates (6) was used for the determination of PAH. The effect of blood pressure reduction on glomerular filtration rate (GFR) and on water and electrolyte excretion was determined on ten of the normal subjects (Group A, Table II); on five of the patients (Group B, Table II) with hypertension but relatively normal kidney function as determined by a GFR[3] of more than 80 ml. per minute; and on 11 of the patients (Group C, Table II) with hypertension and moderate to marked renal damage as determined by GFR[3] less than 80 ml. per minute. Glomerular filtration (GFR) was determined in all patients by the inulin clearance method at plasma levels of 30 to 60 mg. per 100 ml. of plasma. Roe's analytical technique was used (7). Plasma sodium and potassium concentrations and the amounts of these electrolytes excreted in the urine were determined using a Beckman flame photometer for analysis. Electrolyte excretion was not determined on the patients on whom TmPAH studies were done because of the diuretic effect of PAH and because this agent increases urinary sodium excretion, thus obscuring any effect due to the hexamethonium.

The blood pressure was determined by the auscultatory method as well as by intra-arterial manometry. In a few patients on whom auscultatory observations alone were made, the mean blood pressure was calculated by the diastolic blood pressure plus one-third of the pulse pressure. The intra-arterial needle was connected to a mercury manometer through a manifold which was also used for collecting blood samples. Blood for analysis was collected two minutes prior to the midpoint of each 10-minute collection period. A mercury pump (8) was used for maintaining a constant intravenous infusion of inulin and PAH. Rising or unchanging blood levels of inulin and PAH were used. Experiments showing falling blood levels were discarded. Urine samples were obtained through an indwelling catheter using air and 100 ml. of distilled water as a bladder wash. Following the priming doses of PAH and inulin, a 30-minute equilibration period was allowed before the experiment was started. Control observations consisted of three or four consecutive 10-minute periods. Following the control studies, hexamethonium was administered slowly by the intravenous route over a 10- to 20-minute period. The dose of hexamethonium was determined largely by the blood pressure response to the drug. In the hypertensive patients, an attempt was made to reduce the mean blood pressure 20 to 30 mm. of Hg or more, unless the patient experienced uncomfortable side reactions. The mean blood pressure was reduced approximately 10 to 20 mm. of Hg in the normal control subjects. Renal function studies (10-minute periods) were carried out during the

[1] Supported in part by a grant from the National Institutes of Health, Public Health Service, Burroughs Wellcome and Company and the Houston Heart Association.

[2] Supplied through the courtesy of Burroughs Wellcome and Company and Ciba Pharmaceutical Products, Inc.

[3] Corrected to standard body area (1.73 sq. m.).

drug administration and for one to two hours thereafter. Five patients were studied for three hours.

In addition to the previous studies, the effect of norepinephrine infusion after hexamethonium was determined on nine patients. Norepinephrine was given to two of these patients as a therapeutic measure. The study was conducted on the remaining seven only for purposes of evaluating renal hemodynamic response. In this phase of the study, the control renal function observations were carried out as outlined above. When maximum hypotension was established and the blood pressure stabilized for 30 minutes (Patients Nos. 1 and 2 excepted) or more, norepinephrine was administered by continuous infusion using a concentration of 4 micrograms per ml. of 5 per cent glucose. The height of the blood pressure was regulated by the rate of infusion. Renal function studies were then repeated using the same technique as previously outlined.

RESULTS

The blood pressure response to the intravenous administration of hexamethonium in one of the patients is seen in Figure 1. Within ten minutes there was a sharp reduction in blood pressure in most patients, followed by a slight rise and then stabilization at a point somewhat above the lowest level attained. In a few patients the blood pressure decreased slowly and progressively over a 10- to 20-minute period. A reduction in blood pressure was obtained in all patients included in the present study. However, three additional patients who received the drug were not included because there were no significant alterations in blood pressure or in renal function. The percentile reduction in systolic and diastolic pressures were about equal with a resultant decrease in pulse pressure. There was no significant increase in pulse rate. The blood pressure in most of the patients remained at this reduced level for one hour or more and then slowly rose so that after three to four hours it was back to or approaching the control level. However, in some patients, a significant reduction in blood pressure persisted for eight to 12 hours (Figure 1). The effects of hexamethonium on blood pressure and pulse rate are summarized in Table I. The average percentile reduction in blood pressure was about as great in the patients with normal blood pressure as in the hypertensive patients. However, in absolute terms the decrease was twice as great in the patients with hypertension. The average patient without renal disease (Group B) required less hexamethonium than the average patient with renal disease (Group C), but more of the patients with severe and malignant hypertensive vascular disease fell into the latter group. The more rapid the rate of hexa-

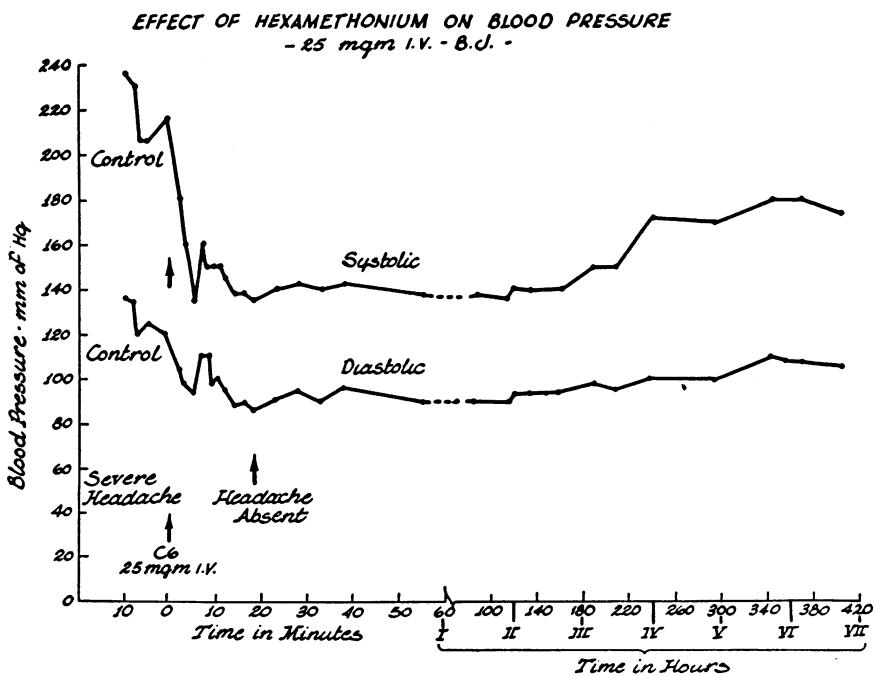


FIG. 1. TYPICAL BLOOD PRESSURE RESPONSE TO INTRAVENOUS HEXAMETHONIUM

TABLE I

Effect of hexamethonium on blood pressure and pulse rate

	MBP*				PR†				
	C	D_1	D_2	D_3	C	D_1	D_2	D_3	Dose‡
	Group A. Control subjects with normal blood pressures								
Ph.	93	87	69	85	84	90	84	—	25
Si.	89	77	77	81	106	120	118	102	25
Al.	97	82	75	88	84	80	84	—	15
Co.	81	75	68	73	68	80	76	76	25
Jo.	84	78	71	77	—	—	—	—	50
Jn.	84	70	77	77	68	76	80	74	10
Ca.	105	83	86	102	92	84	82	84	25
Sc.	105	95	99	96	84	90	84	78	30
Ra.	78	66	71	74	92	88	84	80	25
Jd.	94	77	76	77	90	78	76	80	25
Mean	91	79	77	83	85	87	85	82	26
% of Control		87	85	91		102	100	96	—
	Group B. Hypertensive patients with minimal renal change, i.e., GFR more than 80 ml./min.								
Jo.	139	125	105	100	—	—	—	—	20
Wa.	169	123	122	125	88	88	88	88	20
Ha.	141	120	110	121	92	104	100	104	10
Ro.	143	100	97	98	—	—	—	—	25
Mo.	147	137	119	123	80	76	80	84	10
Mean	148	121	111	113	87	89	89	92	17
% of Control		82	75	76		102	102	106	—
	Group C. Hypertensive patients with renal damage, i.e., GFR less than 80 ml./min.								
Cr.	170	132	134	142	—	—	—	—	5
Ca.	143	120	98	98	—	—	—	—	25
Ha.	191	157	174	184	—	—	—	—	25
St.	166	130	122	122	—	—	—	—	45
Wo.	146	129	130	135	—	—	—	—	60
Ha.	153	104	111	133	88	88	80	80	20
Nu.	151	136	129	130	—	—	—	—	50
Mc.	156	147	145	143	88	88	84	84	20
Hr.	146	114	103	124	84	92	84	92	40
Pe.	176	166	157	160	72	28	80	76	75
Sa.	129	86	81	88	92	88	94	84	25
Mean	157	129	126	133	85	77	84	83	35
% of Control		82	80	85		91	99	98	—

* MBP—Mean blood pressure, diastolic plus one-third of the pulse pressure.
† PR—Pulse rate.
‡ Dose—milligrams given parenterally.
C—Control.
D_1—During intravenous infusion of hexamethonium, 10- to 20-minute period.
D_2—Average of two periods during maximum reduction in blood pressure after completion of D_1.
D_3—One hour after hexamethonium infusion.

methonium administration the more precipitous was the reduction in blood pressure. It was a common observation that initially the infusion of the drug caused a progressive reduction in blood pressure until a floor in the blood pressure was reached. At this point, maximal blockade for this drug was apparently approached and considerably greater amounts of hexamethonium could be given without bringing about much more of a reduction in blood pressure. Usually there was no great difference in the mean blood pressure during the drug infusion (D_1) (after initial reduction), at the point of maximum depression (D_2), and one hour after giving hexamethonium (D_3) both in the normotensive and the hypertensive patients. In several instances the mean blood pressure was lower during the period of drug infusion (D_1) than at any time thereafter (D_2).

Associated with the blood pressure reduction, there was a sharp decrease in GFR (Table II)

during the period of 10 to 20 minutes while the hexamethonium was being administered (period D_1). When compared with the mean of the control observations, the mean value for GFR during this period (D_1) showed a greater percentile reduction in the patients with hypertension (Groups B and C) than in the normals (Group A), although the percentile reduction in mean blood pressure was about equal. However, following the drug, the absolute blood pressure was con-

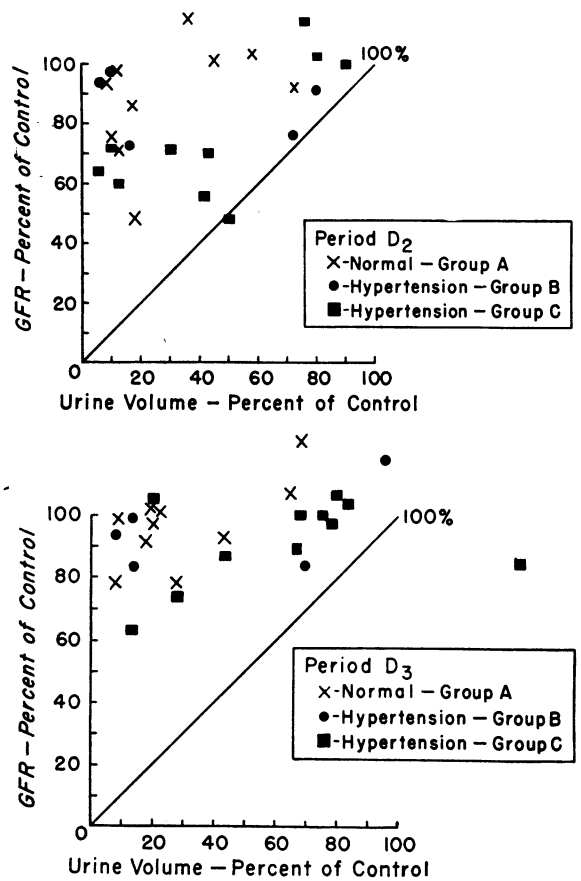
TABLE II

Effect of blood pressure reduction with hexamethonium on glomerular filtration rate and on the rate of excretion of sodium, potassium, and water by the kidney

Pt.	GFR* C	GFR* D_1	GFR* D_2	GFR* D_3	UV† C	UV† D_1	UV† D_2	UV† D_3	Na Excr.‡ C	Na Excr.‡ D_1	Na Excr.‡ D_2	Na Excr.‡ D_3	K Excr.§ C	K Excr.§ D_1	K Excr.§ D_2	K Excr.§ D_3	U/P In.¶ C	U/P In.¶ D_1	U/P In.¶ D_2	U/P In.¶ D_3
Group A. Control patients with normal blood pressure																				
Ph.	87	96	41	—	1.1	1.5	0.2	0.3	3.67	4.02	0.74	—	2.12	2.00	1.16	—	84	80	289	—
Si.	114	84	85	89	7.5	1.7	0.7	0.6	5.87	3.52	3.21	4.68	1.78	1.45	1.65	1.85	17	69	163	170
Al.	120	88	85	116	8.5	1.1	1.0	1.7	2.46	1.02	1.11	1.76	2.33	1.80	3.39	—	10	29	34	—
Co.	121	125	104	110	4.8	4.9	0.8	0.9	5.22	4.31	1.43	—	3.37	2.91	3.18	3.76	25	27	136	121
Jo.	121	128	113	112	8.3	9.1	6.0	3.6	8.68	7.23	5.25	6.54	3.29	3.11	2.86	3.33	15	14	20	32
Jn.	104	105	108	106	14.4	11.8	8.3	3.2	3.38	1.32	1.20	2.34	3.62	3.40	3.20	—	9	11	16	—
Ca.	109	45	125	135	2.5	0.6	0.9	1.7	3.88	1.48	0.76	1.40	3.46	1.38	5.53	5.50	50	75	152	79
Sc.	103	83	101	105	5.7	1.1	0.6	1.2	4.45	2.00	3.20	3.40	4.40	5.70	5.55	5.64	18	73	162	—
Ra.	163	166	167	175	15.0	7.2	6.7	9.7	4.62	1.98	2.04	3.58	1.96	2.06	3.12	3.29	11	25	26	18
Jd.	140	126	132	137	19.2	4.2	1.8	1.8	3.88	1.61	1.94	2.50	2.75	2.38	2.48	2.49	8	27	77	76
Mean	118	105	106	121‖	8.7	4.3	2.7	2.5	4.61	2.85	2.09	3.28‖	2.91	2.62	3.21	3.69‖	25	43	108	83‖
% of Control		89	90	103		49	31	29		62	45	71		90	110	127		172	432	332
Plasma Sodium (mEq.) same periods (mean—10 pts.)									146	148	147	148								
Group B. Hypertensive patients with minimal renal damage, i.e., GFR more than 80 ml./min.																				
Jo.	140	69	136	138	10.1	3.7	1.0	1.3	2.82	3.00	0.85	0.98	4.36	3.46	4.02	4.78	13	23	132	94
Wa.	81	28	62	68	16.8	12.5	12.3	11.8	6.28	3.65	4.74	4.60	1.25	1.33	1.45	1.60	5	2	5	6
Ha.	85	84	77	100	11.4	9.3	9.1	11.0	5.28	3.03	3.73	4.00	1.31	1.36	1.26	1.42	7	9	8	10
Ro.	140	38	131	130	9.9	1.1	0.9	0.8	7.47	1.50	1.23	0.93	2.72	4.35	3.26	3.38	16	42	145	180
Mo.	103	64	74	86	4.3	0.8	0.7	0.6	15.61	7.92	6.16	5.75	6.39	2.30	3.62	6.90	26	90	120	162
Mean	110	57	96	104	10.5	5.5	4.8	5.1	7.49	3.82	3.34	3.25	3.21	2.56	2.72	3.62	13	33	82	90
% of Control		52	87	95		52	46	49		51	45	43		80	85	113		254	631	692
Plasma Sodium (mEq.) same periods (mean—5 pts.)									147	150	148	147								
Group C. Hypertensive patients with renal damage, i.e., GFR less than 80 ml./min.																				
Cr.	67	45	69	60	1.2	0.8	1.0	0.8	1.42	0.78	1.00	1.29	2.11	1.45	2.98	2.30	52	53	64	66
Ca.	21	24	12	22	1.0	0.9	0.4	0.8	1.10	1.55	0.22	0.25	2.42	2.78	1.35	1.20	23	17	19	24
Ha.	33	17	23	33	7.4	2.0	3.2	5.8	7.15	1.54	2.22	4.78	1.74	0.92	1.20	1.24	4	8	7	5
St.	58	34	35	37	8.6	0.7	1.0	1.1	6.80	1.52	0.60	0.64	2.18	1.20	0.66	0.64	8	59	38	36
Wo.	24	16	17	18	5.4	1.5	1.6	1.5	2.84	0.78	1.46	1.42	1.59	1.56	1.72	1.64	5	12	10	12
Ha.	38	20	28	39	6.0	0.2	0.6	1.2	3.18	0.35	0.60	1.66	1.66	1.25	1.58	1.91	6	95	43	28
Nu.	8	7	8	8	2.2	2.1	2.0	1.5	1.99	1.89	1.97	1.60	1.71	1.68	1.88	1.84	4	3	5	6
Mc.	7	7	8	7	2.0	0.8	1.5	1.5	4.40	3.52	4.00	4.64	1.15	0.97	1.21	1.42	4	8	5	4
Hr.	66	36	42	59	6.6	1.3	0.3	2.9	3.08	1.10	2.00	2.47	3.43	3.50	3.70	3.60	10	25	130	—
Pe.	34	37	26	37	7.4	7.4	—	5.9	2.68	3.99	3.43	3.89	2.07	2.59	2.94	2.91	24	6	—	8
Sa.	39	18	19	33	0.6	0.4	0.3	1.0	0.34	0.19	0.19	0.54	3.30	1.90	1.95	3.80	58	40	65	24
Mean	36	24	26	32	4.4	1.6	1.2	2.2	3.18	1.56	1.61	2.11	2.12	1.80	1.92	2.05	18	30	39	21
% of Control		67	72	89		36	27	50		49	51	66		85	91	97		167	217	117
Plasma Sodium (mEq.) same periods (mean—11 pts.)									142	141	142	144								

* GFR—Glomerular filtration rate, ml./minute—corrected to standard body area.
† UV—Urine volume, ml./minute.
‡ Na excr.—Sodium excretion, mg./minute.
§ K excr.—Potassium excretion, mg./minute.
¶ U/P in.—Urine concentration Inulin/Plasma concentration Inulin.
‖ Average control values for patients in D_3 series: GFR = 122; Na excr. = 4.65 mg.; K excr. = 3.00 mg.; and U/P inulin = 21.
C—Control.
D_1—During intravenous infusion of hexamethonium, 10- to 20-minute period.
D_2—Average of two periods during maximum reduction in blood pressure after completion of D_1.
D_3—One hour after hexamethonium infusion (average values for 2 periods).

siderably lower in the normal individuals (average MBP = 79 mm. Hg) than in the two groups of hypertensive patients (average MBP = 121 and 129 mm. Hg). The observations on renal function following the period of drug infusion and after maximum hypotension was attained are presented under column D_2, Table II. These values represent the average of two successive 10-minute periods. The one-hour observations (D_3) also represent the average of two successive 10-minute periods. Following the initial acute reduction in glomerular filtration rate (GFR), which was most marked during the period of drug administration, there was a gradual return toward control levels. After one hour, GFR approximated the control observations in the majority of both normotensive and hypertensive patients. In this respect, there was a difference in the hypertensive patients with renal damage and those without. At the point of maximum reduction in blood pressure (D_2) both the normotensive and hypertensive patients with normal renal function apparently adapted to the reduced pressure more rapidly than those with renal damage. As a result, the average GFR for the normal group was 90 per cent of the control; the average GFR for the hypertensive group with normal kidneys (Group B) was 87 per cent of the control; but for the patients with renal damage it was 72 per cent of the average of the control observations. This difference in renal readjustment to the reduced blood pressure could also be noted after one hour. The mean value for GFR in the normal group was 103 per cent of the control, while in the hypertensive patients with renal damage, it was only 89 per cent. The differences in adaption to lowered pressure were greater in some patients than in others since the number of patients in whom GFR failed to return to absolute control levels was about equivalent in both groups. This is of significance in that the excretory capacity as reflected in blood urea nitrogen was already impaired in many of the patients in the latter group. Therefore, only a small reduction in GFR could be expected to depress further (at least temporarily) renal excretory function in contrast to the wide margin of renal excretory reserve which exists in patients with relatively normal kidneys.

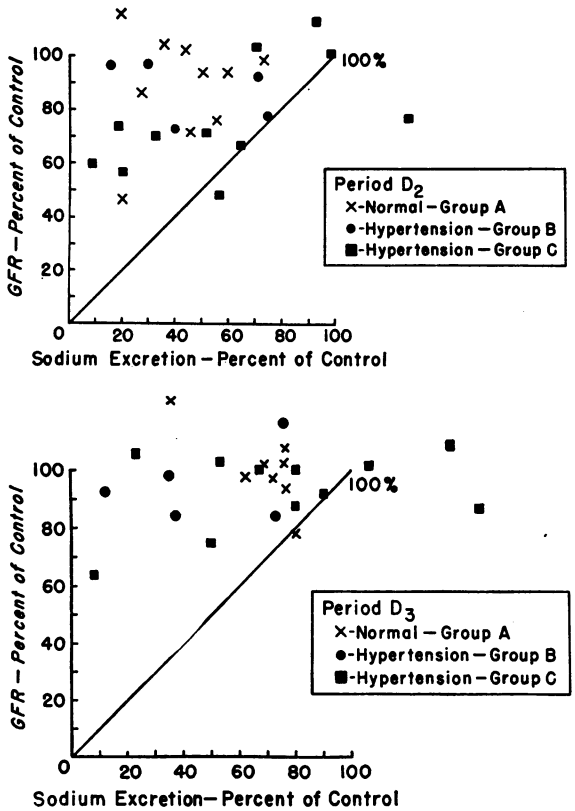


FIGS. 2A AND 2B. GLOMERULAR FILTRATION RATE IS PLOTTED AGAINST URINE VOLUME. THE VALUES ARE EXPRESSED IN PER CENT OF THE CONTROL OBSERVATIONS

Figure 2A represents the observations during maximum reduction in blood pressure (D_2).

Figure 2B represents the observations one hour after the administration of hexamethonium. Urine is reduced more than glomerular filtration rate during both periods of observation. There is essentially no difference between the normal patients and those with hypertensive vascular disease.

The reduction in blood pressure following hexamethonium was associated with a marked antidiuretic effect whether or not glomerular filtration rate (GFR) was reduced. Although GFR was reduced in the majority of patients, renal tubular reabsorption of water was increased out of proportion. This is clearly demonstrated in Figures 2A and 2B in which the GFR for periods D_2 and D_3 is expressed as per cent of control and is plotted against urine volume expressed in the same manner. During period D_2 all the values for GFR except two fell above the line of unity when compared with urine volume, and these two were hypertensive patients in whom GFR and urine volume decreased proportionally. There were

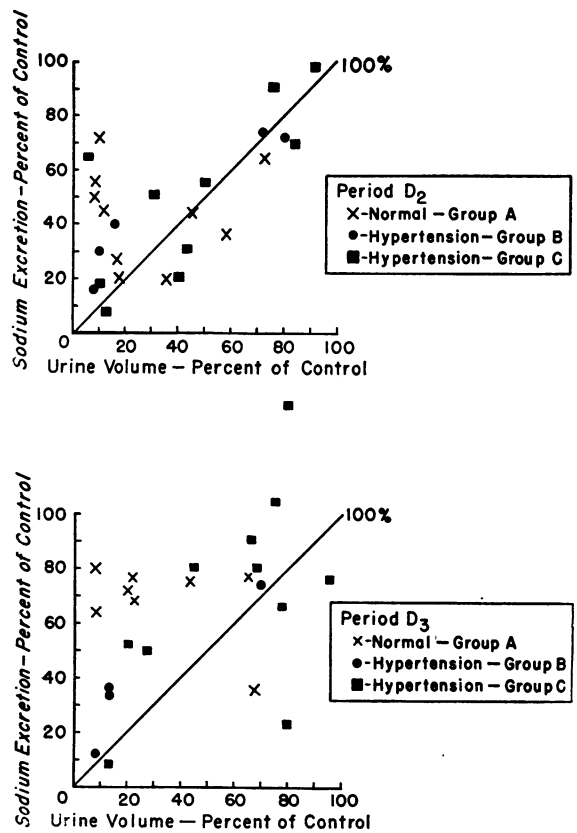


FIGS. 3A AND 3B. URINARY EXCRETION OF SODIUM IS PLOTTED AGAINST GLOMERULAR FILTRATION RATE. THE VALUES ARE EXPRESSED IN PER CENT OF THE CONTROL OBSERVATIONS

Figure 3A includes the observations during maximum reduction in blood pressure and Figure 3B those one hour after the administration of the hexamethonium. Sodium reabsorption is increased out of proportion to the reduction in glomerular filtration rate. One hour after hexamethonium, the glomerular filtration rates are returning toward the control values more rapidly than sodium excretion rates.

no obvious differences between the normotensive and the hypertensive patients and those with and without renal disease. After one hour (D_3) GFR approached or returned to the control values, but the urine volumes remained depressed to about the same degree as during period D_2. There was one exception (Sa., Table II) who was a patient with marked renal damage. In this instance, urine volume after one hour was greater than during the control period. The antidiuretic effect of acute reduction in blood pressure after hexamethonium is also reflected in the increasing U/P ratio of inulin. This was less pronounced in the patients with reduced filtration rate than in the other two groups.

Associated with the antidiuretic effect following hexamethonium, the renal tubules reabsorbed a greater proportion of the filtered sodium, resulting in a decreased excretion of this electrolyte in the urine. This also occurred independently of glomerular filtration rate, which can be visualized in Figures 3A and 3B. Here GFR for each patient is plotted against sodium excretion. Both are expressed in per cent of the control observations. During period D_2 all of the points for GFR but one fell on or above the line of unity when compared with sodium excretion. The exception again was a patient (Pe., Table II) with hypertension and renal damage. After one hour, the points continued



FIGS. 4A AND 4B. URINE VOLUME IS PLOTTED AGAINST SODIUM EXCRETION. THE VALUES ARE EXPRESSED IN PER CENT OF THE CONTROL OBSERVATIONS

During the period of maximum reduction in blood pressure (Figure 4A), urine volume and sodium excretion are decreased proportionally in most patients. This is not true in those patients showing an extreme reduction in urine volume.

to fall above the line of unity (Figure 3B), although there was some increase in sodium excretion. There were two exceptions (Sa. and Pe.), both patients with renal damage. Otherwise, it appeared that the normotensive patients and the hypertensive ones with and without renal damage responded in a similar manner. As a rule, impaired renal function as estimated by reduced GFR did not alter this effect. This response was maximal during the greatest depression in blood pressure (D_2) showing a reduction in sodium excretion of 50 per cent or more for the group.

The relationship between the reduction in urine volume and sodium excretion is graphed in Figures 4A and 4B. During the period of maximum reduction in blood pressure, sodium excretion was reduced in proportion to urine volume unless urine volume was reduced 70 to 80 per cent or more of the control observation. Above this range the points fell on or near the line of unity. Below 70 to 80 per cent the points fell on or above this line, indicating a greater reduction in water excretion than in sodium. This may represent a factor of limitation as far as sodium reabsorption is concerned but might also reflect errors in collection due to the low urine volume. After one hour (D_3) there was much less pattern to the graph (Figure 4B).

The excretion of potassium was depressed in some patients following hexamethonium but this was inconstant. There were no significant alterations in plasma sodium (Table II) and potassium during this study. Observations on five patients two to three hours after hexamethonium administration showed that the renal clearance studies all returned to control values before the blood pressure did.

When the effect of acute blood pressure reduction on maximum tubular function was determined (Table III), the glomerular filtration rate was reduced in essentially the same manner as during the previous studies (Table II). However, maximum tubular excretory capacity of PAH was not altered significantly. This is reflected in a decrease in the GFR/TmPAH ratio. It indicates that the number of functioning nephrons did not change as the blood pressure decreased, either in the normotensive group or in the patients with hypertension. The reduction in GFR resulted from decreased filtration in the active glomeruli. Kidneys showing impaired renal function as defined in this study responded in the same way as in the normal.

The response to norepinephrine after hexamethonium was evaluated in nine patients (Table IV), to two of whom it was given as a therapeutic

TABLE III

Effect of acute blood pressure reduction with hexamethonium on glomerular filtration rate and maximum tubular function

Pt.	MBP*				GFR*				UV*				TmPAH†				GFR/TmPAH			
	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
Patients with hypertension																				
Ta.	108	84	76	88	57	38	47	52	2.9	1.9	2.1	2.1	24	25	27	20	2.37	1.52	1.74	2.60
Jo.	126	106	104	113	55	50	47	51	2.7	2.5	2.7	3.0	28	26	25	30	1.96	1.92	1.88	1.70
Ph.	123	86	76	76	126	91	103	110	7.5	3.9	2.8	3.1	87	74	88	83	1.45	1.23	1.17	1.33
Ma.	178	126	107	112	69	60	48	50	3.0	2.6	2.7	2.6	52	52	58	51	1.33	1.15	0.83	0.98
Cl.	135	109	99	100	41	33	36	40	10.8	7.5	4.4	4.6	27	24	25	32	1.52	1.37	1.44	1.25
Ct.	110	60	65	70	28	16	19	20	4.6	1.9	2.3	2.4	21	20	28	28	1.34	0.80	0.68	0.63
Mean	130	95	88	93	63	48	50	54	5.3	3.4	2.8	3.0	40	37	42	41	1.66	1.33	1.29	1.42
% of Control		73	68	72		76	79	86		64	53	57		93	105	103		80	78	86
Normotensive patients																				
Fi.	94	64	70	90	125	121	129	110	6.1	3.6	3.9	5.0	89	88	93	92	1.40	1.38	1.39	1.20
Fl.	104	93	96	97	108	86	91	105	3.0	3.0	3.0	3.0	76	69	66	77	1.42	1.25	1.38	1.37
Ha.	105	100	99	100	146	132	139	135	6.1	4.1	3.5	3.6	75	78	80	81	1.95	1.69	1.74	1.67
Vi.	82	67	80	80	80	60	74	74	3.2	2.9	3.6	2.3	78	75	80	81	1.03	0.80	0.93	0.92
Mean	96	81	86	92	115	100	108	106	4.6	3.4	3.5	3.5	80	78	80	83	1.45	1.28	1.36	1.29
% of Control		84	90	96		87	94	92		74	76	76		98	100	104		88	94	89

* See Tables I and II for key to abbreviations.

† TmPAH—Maximum tubular excretion of p-aminohippurate, mg./min.

TABLE IV

Renal response to hexamethonium followed by an intravenous infusion of norepinephrine

Pt. No.	MBP* C	MBP* D_H	MBP* D_N	GFR* C	GFR* D_H	GFR* D_N	UV* C	UV* D_H	UV* D_N	TmPAH* C	TmPAH* D_H	TmPAH* D_N
1†	140	63	115	100	0?	82	1.0	0	3.4	66	—	59
2‡	165	95	149	67	13	45	0.9	1.0	0.6	—	—	—
3	173	98	153	23	25	19	5.3	2.4	3.2	—	—	—
4	123	76	140	126	110	112	7.5	3.1	4.2	87	86	83
5	129	103	184	39	30	41	0.6	0.5	3.8	21	28	30
6	139	107	161	140	123	129	—	—	—	—	—	—
7	170	123	174	67	62	57	—	—	—	—	—	—
8	107	68	119	21	22	16	1.0	1.0	0.7	—	—	—
9	180	120	184	75	67	65	3.8	2.8	2.4	57	42	42
Mean	144	95	155	73	50	63	2.9	1.5	2.6	58	52	54

C—Control.

D_H—30 to 60 minutes following hexamethonium given intravenously.

D_N—Norepinephrine infusion following previous blood pressure reduction with hexamethonium.

* See Tables I, II, and III for key to abbreviations.

† This patient developed acute hypotension following oral hexamethonium. Norepinephrine was administered therapeutically.

‡ Patient developed mental confusion and became disoriented following hexamethonium. This improved when the blood pressure was increased with norepinephrine infusion.

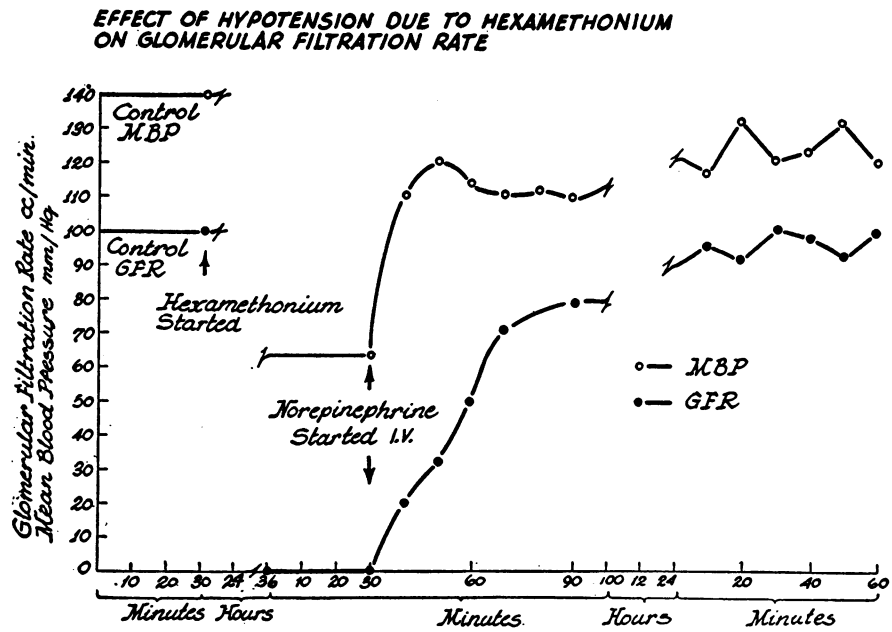


FIG. 5A. FOLLOWING AN OVERDOSE OF HEXAMETHONIUM BY THE ORAL ROUTE, THE SUPINE BLOOD PRESSURE DECREASED FROM 180 MM. HG SYSTOLIC AND 120 MM. HG DIASTOLIC TO 85 SYSTOLIC AND 52 DIASTOLIC

It remained at approximately this level for 2 days and the patient became anuric on the second day. A norepinephrine infusion was started and the blood pressure was increased to 145 systolic and 100 diastolic. Within 15 minutes the patient began to form urine. The glomerular filtration rate gradually increased until after one hour it was approaching the control level.

measure. One of the patients (Patient No. 1, Table IV and Figure 5A) had previously taken an excessive dose of hexamethonium orally, following which the mean blood pressure decreased from 140 to 63 mm. Hg and she became anuric. Renal function was measured during the control period and after the blood pressure was raised with an infusion of norepinephrine. Following an increase in the mean blood pressure to approximately 115 mm. Hg, the GFR and urinary output increased progressively; the hexamethonium was excreted and recovery was uneventful.

In the second patient (Patient No. 2, Table IV and Figure 5B), the mean blood pressure decreased from 165 to 95 mm. Hg following which the patient became mentally confused and disoriented. Glomerular filtration was depressed from 67 to 13 ml. per minute. Norepinephrine was started and the blood pressure increased. Cerebral function returned to the control state and at the same time the GFR increased to 45 ml. per minute (Figure 5B). However, when norepinephrine was discontinued after 20 minutes, the blood pressure and GFR were again depressed. After a second administration of norepinephrine for 20 minutes the blood pressure became better stabilized.

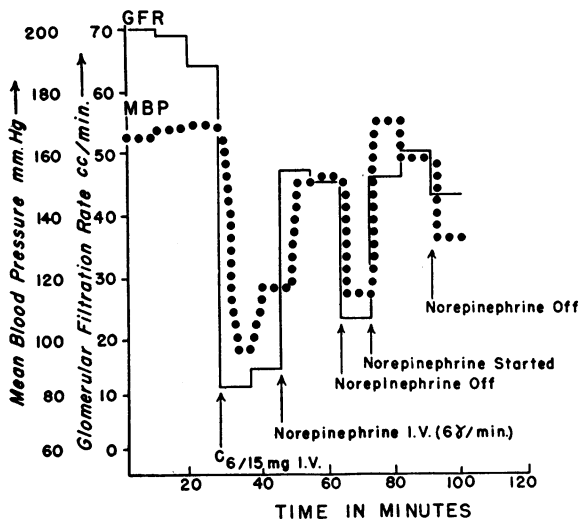


FIG. 5B. THIS PATIENT EXHIBITED SOME ENCEPHALOPATHIC MANIFESTATIONS DURING THE CONTROL PERIOD

Following hexamethonium the mean blood pressure decreased from 165 to 95 mm. Hg and the patient became disoriented. The GFR was markedly depressed (GFR of 67 decreased to 13 ml. per minute). The mean blood pressure was increased with norepinephrine to 149 mm. Hg, whereupon the cerebral manifestations and GFR improved.

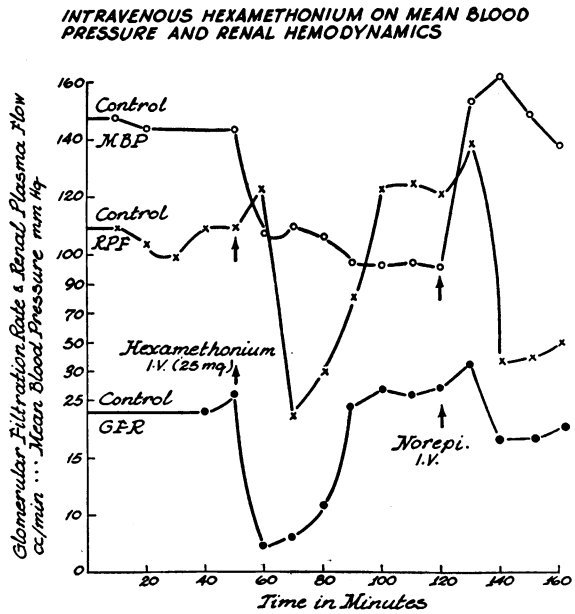


FIG. 5C. THE RENAL HEMODYNAMIC RESPONSE TO PARENTERAL HEXAMETHONIUM IN A PATIENT WITH RENAL DAMAGE (GFR = 23)

There was an acute reduction in blood pressure associated with depression of GFR. The latter gradually returned to the control level despite a maintained reduction in blood pressure. When the blood pressure was increased to the control values with norepinephrine, GFR was slightly depressed.

Norepinephrine was given to seven additional patients in order to evaluate better the renal response under these circumstances. The effect on GFR is variable and appears to be dependent on the degree of depression following the administration of hexamethonium. In general when GFR is markedly depressed by hexamethonium, norepinephrine tends to increase it toward the control values at the same time that the blood pressure is increased (Figures 5A–5B). However, in those patients in whom GFR was not markedly depressed (Figure 5C) from the control period, raising the blood pressure with norepinephrine seemed to have little effect on GFR, or actually reduced it (Figure 5C). In three patients thus studied, TmPAH was not affected significantly by this procedure. Raising the blood pressure with norepinephrine had very little effect on the antidiuretic effect of hexamethonium although sodium excretion was enhanced.

DISCUSSION

The present observations indicate that ganglionic blockade with hexamethonium was a dependable method for reducing the blood pressure in both normotensive and hypertensive individuals. As the blood pressure decreased, there was no associated reflex tachycardia, probably a result of the ganglionic blockade of the sympathetics to the heart. With some exceptions, the marked reduction in blood pressure in patients exhibiting hypertension again emphasizes the importance of the autonomic nervous system in this malady. Associated renal disease did not affect this response, suggesting that even when the kidneys are involved, imbalance of the autonomic nervous system usually plays a significant role in the development of the elevated blood pressure.

The observation of acute depression of glomerular filtration rate (GFR) following ganglionic blockade and blood pressure reduction with hexamethonium is in contrast to similar studies on anesthetized dogs (9). In the latter studies, the initial depression of GFR was not seen, indicating more rapid readjustment of renal hemodynamics in dogs. Likewise, it appears that GFR in patients with normal kidneys tended to readjust to changes in blood pressure more rapidly than it did in patients with damaged ones. However, one hour after the hexamethonium was given, these differences were not so apparent, and very little depression of GFR was noted despite the maintained reduction in blood pressure. This response of patients to hexamethonium is qualitatively similar to autonomic blockade with tetraethylammonium (10). After the latter drug there is also an initial depression of renal function followed by readjustment to a lower blood pressure. Subsequently, renal functions gradually return to control levels.

The renal dynamics in patients with hypertension respond to hexamethonium in essentially the same way as do those in patients with normal blood pressure. Patients with evidence of moderate to severe renal disease react qualitatively in a similar manner. This indicates that the nephrons that remain functional apparently react in a normal fashion and supports the contention that in the damaged kidney nephrons are destroyed as anatomical and functional units. Those nephrons that remain, function in a relatively normal fashion. There is no evidence to indicate why glomerular filtration is reduced and remains depressed in some patients more than others despite equivalent absolute blood pressure reductions in both.

In patients with relatively normal kidneys, as long as the blood pressure is not reduced below critical filtration levels, renal excretory capacity will be adequate, even though GFR may be somewhat depressed. However, when renal excretory capacity and glomerular filtration are already impaired due to anatomical changes in the kidneys, then only slight reductions in GFR may further jeopardize this excretory capacity and thus decompensate the renal mechanism. There seems to be no way to predict which patients will not readjust their renal hemodynamics and filtrating capacity to a lower blood pressure, since some of the patients with the most renal damage readjusted as completely as the normotensive ones, although the former was at a higher absolute level of blood pressure. If the blood pressure in patients with hypertension and renal damage is reduced to the same absolute level as the normotensive patients, then more marked depression of renal function (GFR) may occur. This was seen in several instances in the present study and suggests that in the therapy of hypertension associated with renal damage, treatment should be aimed at post-drug blood pressures somewhat short of normotensive levels. If decreased excretory capacity follows blood pressure reduction with hexamethonium, the pressure should be allowed to increase to such a point that excretory function is not impaired in excess of that which is due to existing anatomical damage. This can best be evaluated on a long-term clinical basis by closely observing the level of blood urea nitrogen. However, the present studies were not designed to establish the long-term therapeutic efficacy of hexamethonium.

The cause of the decreased water and sodium excretion is not apparent. It is not due to an increase in the number of functioning nephrons available for sodium and water reabsorption since TmPAH was not altered by ganglionic blockade and blood pressure reduction. It cannot be explained solely on the basis of reduced glomerular filtration since in many instances it occurred independently of this function. In addition, one

hour after hexamethonium was administered glomerular filtration had returned to the control levels in most of the patients, but a reduction in the rate of water and sodium excretion persisted. It apparently was not due to the liberation of endogenous antidiuretic hormone since this hormone does not increase sodium reabsorption in man (11). Other investigators (12–14) have found that activity of the sympathetic nervous system alters tubular reabsorption of sodium and water. Renal denervation (13) in an unanesthetized dog did not affect GFR or electrolyte excretion, suggesting that the sympathetics had very little to do with this regulatory mechanism when the animal was not under stress. Sartorius and Burlington (14) found an increase in sodium and water excretion following denervation of the kidneys in anesthetized dogs, apparently due to the release of sympathetic neurogenic influences which are present in the anesthetized animal. A similar response was found by Moyer and his associates (9) after autonomic ganglionic blockade with hexamethonium in anesthetized dogs. Because of the possibility that anesthesia may previously have produced a sympathomimetic effect on the dogs' renal dynamics, which was released by ganglionic blockade with hexamethonium, these studies have been repeated on three unanesthetized dogs. The results using the same techniques as previously described are presented in Table V. In these unanesthetized dogs (Table V), GFR and renal plasma flow increased slightly as the blood pressure was reduced in each of the three animals thus studied. This was associated with an increase in sodium excretion. There was no essential difference between these observations and the previous ones using anesthetized animals suggesting that even in the unanesthetized animal, the autonomic nervous system may alter tubular reabsorption of water and electrolytes. These observations as well as the previous ones indicate that sympathetic neurogenic impulses to the kidney may cause an increase in tubular reabsorption of sodium and water in the dog. This is in contrast to the response of the patients observed in the current study, wherein ganglionic blockade (partial) enhanced sodium and water reabsorption rather than decreased it. It is possible that sodium and water excretion was depressed after hexamethonium was given because of sympathetic stimulation to the renal nerves, a result of the renal nerve ganglia not being blocked as completely as were the vasoconstrictor nerves elsewhere, thus causing a differential in vasoconstrictor activity within the sympathetic nervous system. In this instance, reflex vasoconstrictor impulses would emanate over the renal nerves as the blood pressure decreased, thus producing an initial sympathomimetic effect on the kidney. Vasoconstrictive impulses of this nature would also explain the initial reduction in glomerular filtration which occurred but which returned to normal despite a maintained reduction in blood pressure. If this were so, the difference in response between the present studies and the previous observations on dogs would merely indicate less complete blockade in the humans. However, it is quite possible that the difference in the type of response may be due to species differences.

Observations in the present study indicate very little, if any, inhibition of potassium excretion. It is of interest to note that potassium excretion did

TABLE V

Effect of hexamethonium on renal hemodynamics, electrolyte and water excretion of unanesthetized dogs

Dog No.	GFR		RPF		Na Excr.*		K Excr.*		UV†		BP	
	C	D	C	D	C	D	C	D	C	D	C	D
1	29	39	104	166	0.10	1.82	0.64	1.75	0.4	1.3	125	100
2	53	58	112	130	0.25	1.19	0.27	2.45	3.6	1.6	165	120
3	43	48	130	167	0.16	1.31	0.36	3.30	2.9	1.4	150	125
Mean	42	48	115	154	0.17	1.44	0.42	2.50	2.3	1.4	147	115

C—Control.
D—Average of 2 successive periods after hexamethonium.
BP—Mean blood pressure, mm. Hg.
* Milligrams per minute.
† UV, urine volume, ml. per minute.

not change as the urine volume decreased, indicating that potassium reabsorption did not follow the same pattern as sodium. It also indicates that changes in potassium excretion were not dependent on changes in urine volume in this instance. Otherwise, potassium excretion would have more closely paralleled the changes in urine volume.

SUMMARY AND CONCLUSIONS

1. Hexamethonium is an effective autonomic ganglionic blocking agent for reducing the blood pressure in both normotensive and hypertensive patients. The percentile reduction in systolic and diastolic blood pressures is about equal.

2. When the blood pressure is reduced with parenteral hexamethonium, there is an immediate reduction in glomerular filtration rate, sodium excretion and water excretion. However, after one hour, despite a maintained reduction in blood pressure, glomerular filtration rate returns to or approximates the control values. The antidiuretic effect persists but sodium excretion increases. At the point of maximum depression of blood pressure (D_2) there is not a consistent relationship between the reduction in glomerular filtration rate and the decreased excretion of water and sodium. Urine volume and sodium excretion are depressed proportionally until the urine volume is decreased to 20 to 30 per cent of the control values or less, and then the urine volume decreases more than sodium excretion. The initial effect on the kidney has the appearance of sympathetic renal nerve stimulation.

3. Kidneys showing marked impairment of renal function respond to blood pressure reduction with hexamethonium in essentially the same way as do normal ones, indicating that the nephrons are destroyed as anatomical units, and those that remain, function in a relatively normal fashion. However, this adjustment in patients with renal damage occurs more slowly than it does in patients with normal renal function.

4. The decrease in glomerular filtration following hexamethonium is not due to a decrease in the number of functioning nephrons since maximum tubular function (TmPAH) is not altered.

5. Moderate reduction in the blood pressure of patients with moderate to marked impairment of renal function is feasible. In most instances the functional nephrons that remain in damaged kidneys show a slower but a relatively normal hemodynamic readjustment to a lowered blood pressure.

6. After reduction in blood pressure with hexamethonium, norepinephrine is an effective vasopressor agent. The effect of norepinephrine on glomerular filtration under these circumstances is variable. If the reduction in blood pressure is excessive and glomerular filtration markedly depressed, raising the blood pressure with norepinephrine increases the filtration. If glomerular filtration is not depressed as a result of hexamethonium, increasing the blood pressure with norepinephrine does not affect or may slightly reduce glomerular filtration.

REFERENCES

1. Freis, E. D., Finnerty, F. A., Schnaper, H. W., and Johnson, R. L., The treatment of hypertension with hexamethonium. Circulation, 1952, **5**, 20.
2. Johnson, I., Moyer, J. H., Mills, L. C., and Miller, S. I., Treatment of hypertension; results with hexamethonium salts administered orally. Texas State J. Med., 1952, **48**, 331.
3. Schroeder, H. A., Control of hypertension by hexamethonium and 1-hydrazinophthalazine. Arch. Int. Med., 1952, **89**, 523.
4. Hafkenschiel, J. H., Crumpton, C. W., Moyer, J. H., and Jeffers, W. A., The effects of dihydroergocornine on the cerebral circulation of patients with essential hypertension. J. Clin. Invest., 1950, **29**, 408.
5. Moyer, J. H., Miller, S. I., Tashnek, A. B., Snyder, H., and Bowman, R. O., Malignant hypertension and hypertensive encephalopathy—cerebral hemodynamic studies and therapeutic response to continuous infusion of intravenous Veriloid. Am. J. Med., in press.
6. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Graber, M., The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. Clin. Invest., 1945, **24**, 388.
7. Roe, J. H., Epstein, J. H., and Goldstein, N. P., A photometric method for the determination of inulin in plasma and urine. J. Biol. Chem., 1949, **178**, 839.
8. Sirota, J. H., Baldwin, D. S., and Villarreal, H., Diurnal variations of renal function in man. J. Clin. Invest., 1950, **29**, 187.
9. Moyer, J. H., Huggins, R. A., Handley, C. A., and Mills, L. C., Effect of hexamethonium chloride on cardiovascular and renal hemodynamics and on electrolyte excretion. J. Pharmacol. & Exper. Therap., 1952, **106**, 157.

10. Hoobler, S. W., Moe, G. K., Rennick, B. R., Neligh, R. B., and Lyons, R. H., The effect of autonomic blockade with tetraethylammonium on the renal circulation in dogs and in normal and hypertensive patients. Michigan University. Univ. Hosp. Bull., Ann Arbor, 1947, **13**, 9.
11. Murphy, R. J. F., and Stead, E. A., Jr., Effects of exogenous and endogenous posterior pituitary antidiuretic hormone on water and electrolyte excretion. J. Clin. Invest., 1951, **30**, 1055.
12. Nickel, J. F., Smythe, C. M., and Bradley, S. E., Effect of pressor agents on renal water and electrolyte excretion in man. Federation Proc., 1952, **11**, 113.
13. Surtshin, A., Mueller, C. B., and White, H. L., Effect of acute changes in glomerular filtration rate on water and electrolyte excretion. Federation Proc., 1952, **11**, 157.
14. Sartorius, O. W., and Burlington, H., Effects of denervation on renal function in the dog. Federation Proc., 1952, **11**, 137.