Journal of Clinical Investigation
Vol. 41, No. 2, 1962

REACTIVITY OF RENAL AND SYSTEMIC CIRCULATIONS TO VASOCONSTRICTOR AGENTS IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS*

By ERVIN A. GOMBOS,† WILLIAM H. HULET,‡ PIERRE BOPP,§ WILLIAM GOLDRING, DAVID S. BALDWIN AND HERBERT CHASIS

(From the Department of Medicine, New York University School of Medicine and the Third and Fourth (NYU) Medical Divisions, Bellevue Hospital, New York, N. Y.)

(Submitted for publication June 13, 1961; accepted August 31, 1961)

It has been suggested that vascular hyper-reactivity is in part responsible for the vasoconstriction in human essential hypertension. This thesis has been examined by comparing the response to vasoconstrictor agents in hypertensive patients with that of normotensive subjects.

Kylin (1), Brems (2), Gordon and Levitt (3), Fatherree and Hines (4), Judson and co-workers (5, 6), and Barany and James (7) failed to demonstrate increased sensitivity to epinephrine or norepinephrine as measured by systemic blood pressure response in hypertensive patients. Goldenberg and associates (8) found no increased response to norepinephrine in hypertensive patients at high dosage but the response was somewhat increased at lower dosage. However, increased response of systemic blood pressure to epinephrine and norepinephrine in hypertension was reported by Clough (9), Jensen (10), and Doyle and Black (11).

In evaluating sensitivity of local vascular beds of the extremities to epinephrine by calorimetric or plethysmographic methods, Pickering and Kissin (12) and Prinzmetal and Wilson (13) found no increased response in hypertensive patients. Contrariwise, Mendlowitz and Naftchi (14), Barany and James (7), and Doyle, Fraser and Marshall (15) reported increased reactivity in hypertension; Duff (16) reported no increased sensitivity to epinephrine in "benign hypertension" but increased reactivity in "progressive or malignant hypertension." Greisman (17) found that the capillary bed of the nailfold of patients with essential hypertension was hyperreactive to infused *l*-norepinephrine. In normotensive subjects several investigators (18–20) have shown that epinephrine and *l*-norepinephrine produce reduction in renal plasma flow without affecting glomerular filtration rate. However, sensitivity of the renal vascular bed to epinephrine and *l*-norepinephrine has not been studied in subjects with essential hypertension.

The relationship of sodium intake to blood pressure levels in hypertensive patients has suggested the possibility that vascular resistance and reactivity may be affected by sodium content of the body or, specifically, the vessel wall. Raab and colleagues (21) observed a weakened or abolished pressor effect of infused epinephrine and *l*-norepinephrine in hypertensive patients on a rice diet. Aleksandrow and co-workers (22), induced salt depletion in hypertensive subjects by administration of chlorothiazide, and also observed reduction of the pressor effect of infused *l*-norepinephrine. Dahl (23), on the other hand, failed to demonstrate a uniform decrease in pressor response to *l*-norepinephrine after sodium depletion accomplished by dietary restriction in hypertensive patients. None of these studies dealing with the effect of sodium depletion on vascular reactivity includes observations on renal hemodynamics.

This paper deals with observations on the vasoconstrictor effect of infused epinephrine and *l*-norepinephrine on the renal and systemic circulations in normotensive and hypertensive subjects during normal sodium intake as well as after a period of dietary sodium restriction. The data demonstrate that renal and systemic arteriolar vasoconstrictor reactivity is equal in normotensive and hypertensive subjects as shown by an equal relative in-

* This study was supported in part by funds from the Joseph Laffan Morse Foundation and the Abraham S. Birsh Fellowship Fund, and United States Public Health Service Grant H-3272, National Heart Institute, Bethesda, Md.

† Research Fellow, New York Heart Association.

‡ Research Fellow, American Heart Association.

§ Abraham S. Birsh Fellow.

TABLE I

Effect of l-norepinephrine on renal and systemic hemodynamics in normotensive and hypertensive subjects on regular salt intake *

Subject† Age	l-Norepinephrine	Urine volume	GFR	RPF	FF	RR	P_m	Pulse
yrs	*μg/min/1.73 m²*	*ml/min*	*ml/min*	*ml/min*	*%*	*dynes-sec-cm⁻⁵*	*mm Hg*	*rate/min*
			Normotensive subjects					
M.S.	Control	3.70	122	602	20.3	5,070	77	94
39	4.9	2.73	131	591	22.1	6,100	91	80
	13.2	4.78	122	490	25.1	8,830	107	79
	21.4	7.61	117	410	28.6	12,000	120	75
	42.4	9.58	127	373	34.0	14,500	131	77
O.V.	Control	0.92	118	621	19.1	4,810	88	74
35	2.6	0.85	105	507	20.8	6,170	92	76
	6.6	0.96	121	512	23.7	6,500	97	68
	12.3	0.85	118	430	27.5	8,350	104	66
	20.0	1.08	130	407	32.0	10,200	116	63
M.So.	Control	1.95	118	604	19.5	5,560	79	92
45	3.0	2.04	120	571	21.0	6,810	90	96
	4.6	2.37	127	505	25.1	8,870	102	90
	7.5	2.34	126	483	26.0	9,880	108	88
	13.9	1.42	104	409	25.9	12,400	114	78
A.B.	Control	5.57	118	709	16.6	4,520	86	110
19	4.6	9.16	121	646	18.7	5,420	93	100
	7.6	10.2	122	582	20.9	6,810	104	72
	13.9	4.43	105	449	23.4	8,940	105	72
	22.8	3.95	95.4	348	27.4	12,500	113	66
M.H.	Control	1.44	157	616	25.6	5,180	83	80
32	8.5	8.18	152	530	28.7	9,000	119	72
	13.8	5.09	157	505	31.1	9,900	124	60
	23.0	3.80	154	445	34.6	12,500	137	56
	30.5	4.07	147	435	33.8	14,600	155	47
V.C.	Control	0.54	133	773	16.8	3,910	79	80
29	6.6	0.57	132	610	21.7	5,810	91	74
	12.1	0.76	129	530	24.3	7,850	105	70
	19.1	1.99	118	460	25.7	8,660		75
	22.6	5.43	121	435	27.8	11,000	120	68
	30.1	9.15	131	447	29.3	13,500	148	70
G.S.	Control	0.96	147	888	16.6	4,120	93	78
33	13.6	1.52	141	641	22.0	7,430	119	66
	21.8	4.54	143	521	27.5	10,200	131	56
	31.5	5.54	119	403	29.5	14,350	142	52
	36.5	5.51	113	355	31.9	16,900	147	50
D.J.	Control	1.45	134	739	18.1	4,220	81	64
23	8.0	4.53	139	636	22.2	5,650	92	62
	14.9	6.99	130	506	25.7	8,060	103	61
	24.0	8.33	128	464	27.6	10,300	119	60
	34.5	7.69	129	426	30.3	11,200	119	59
	40.5	7.48	136	425	32.0	12,000	126	58
H.H.	Control		150	641	23.5	5,530	91	81
31	8.8	7.45	141	511	27.6	8,400	108	67
	16.5	7.54	136	410	33.2	13,900	140	51
M.J.	Control	0.58	134	719	18.6	6,800	107	84
40	4.9	0.66	140	623	22.4	8,610	114	82
	11.2	0.97	135	596	22.6	9,840	125	79

* Clearance values are corrected to 1.73 m² body surface area. See Methods section for abbreviations.
† All subjects are females.

TABLE I—(*Continued*)

Subject† Age	*l*-Norepinephrine	Urine volume	GFR	RPF	FF	RR	P_m	Pulse
yrs	*μg/min/1.73 m²*	*ml/min*	*ml/min*	*ml/min*	%	*dynes-sec-cm⁻⁵*	*mm Hg*	*rate/min*
S.R.	Control	5.11	132	858	15.4	3,790	84	83
30	6.6	5.05	139	735	18.9	5,020	94	77
	10.9	6.20	126	554	22.7	7,450	104	73
	17.9	4.92	116	431	26.9	9,800	107	64
	23.8	4.92	114	400	28.5	11,300	113	61
	28.6	6.28	118	431	27.4	11,200	120	60
D.L.	Control	3.70	121	619	19.7	4,540	74	85
29	6.9	3.62	120	521	23.0	6,470	87	74
	14.6	7.65	120	431	27.9	8,850	97	68
	20.9	5.21	101	332	30.4	11,900	100	60
	24.4	2.79	122	362	33.7	11,800	107	60
	41.8	5.36	116	345	33.6	13,200	114	60
H.V.	Control	2.29	145	809	18.0	4,980	102	83
42	4.8	3.10	150	687	21.9	7,880	133	60
	9.6	8.60	159	625	25.4	9,750	149	58
			Hypertensive patients					
T.B.	Control	1.37	132	474	27.8	12,700	147	80
55	3.1	6.66	122	427	28.5	14,620	159	72
	9.2	9.26	122	413	29.5	16,870	169	72
L.C.	Control	1.24	94.5	583	16.2	7,600	111	96
31	1.4	1.38	97.5	563	17.3	8,400	118	96
	3.0	1.25	94.6	521	18.2	9,500	123	88
	7.4	1.12	92.7	486	20.8	11,800	130	66
I.F.	Control	0.96	87.9	463	19.0	10,000	114	84
49	3.6	1.67	100	456	22.0	12,300	135	85
	5.9	2.84	111	459	24.3	13,200	146	80
	11.1	5.92	115	395	25.4	13,400	166	74
	18.1	11.5	114	356	32.2	20,700	175	88
E.H.	Control	4.93	129	567	22.8	7,650	109	80
42	1.6	8.60	138	555	24.8	8,130	113	78
	2.5	7.96	128	493	26.0	9,340	115	64
	4.8	7.52	127	457	27.8	11,300	128	57
	8.4	4.88	132	457	29.0	12,100	136	52
C.H.	Control	0.93	121	508	23.8	9,260	105	84
43	3.0	0.93	123	464	26.6	11,300	116	83
	4.9	0.92	117	413	28.5	13,900	126	80
	9.1	0.94	121	408	29.8	14,000	126	77
	14.7	1.05	132	383	34.4	16,700	140	77
R.M.	Control	1.71	92.0	399	23.1	11,900	118	68
63	5.3	2.94	103	400	25.7	14,600	133	66
	12.2	4.43	95.6	326	29.4	20,300	161	72
	19.8	3.89	77.4	244	31.6	30,900	182	86
M.L.	Control	1.11	115	531	21.7	8,500	113	89
26	3.4	1.21	117	538	21.7	8,550	115	83
	8.7	2.45	117	461	25.3	11,200	128	70
	12.1	6.18	119	423	28.1	12,800	135	67
	20.1	6.90	115	395	29.1	14,400	140	65

crease in both renal resistance and systemic blood pressure in response to the administration of epinephrine and *l*-norepinephrine. Sodium restriction failed to decrease reactivity of the renal or systemic circulations to these constrictor agents.

METHODS

Observations were made in 16 normotensive subjects without evidence of cardiovascular renal disease and in 16 patients with essential hypertension selected from the wards of the New York University Services of Bellevue Hospital. Hypertensive patients were selected in the

TABLE II

Effect of epinephrine on renal and systemic hemodynamics in normotensive and hypertensive subjects on regular salt intake *

Subject† Age	Epinephrine	Urine volume	GFR	RPF	FF	RR	P_m	Pulse
yrs	*μg/min/ 1.73 m²*	*ml/min*	*ml/min*	*ml/min*	*%*	*dynes-sec-cm⁻⁵*	*mm Hg*	*rate/min*
			Normotensive subjects					
A.B.	Control	4.32	104	655	15.9	4,880	83	103
19	4.7	3.75	105	523	20.0	5,780	79	124
	7.6	4.92	120	560	21.5	5,480	80	130
	14.0	2.62	124	494	25.2	6,660	85	137
	22.8	4.50	137	498	27.6	6,590	85	145
M.So.	Control	2.57	128	531	24.1	8,000	102	107
45	3.0	3.75	133	484	27.4	8,540	98	108
	4.6	6.55	139	501	27.8	8,160	97	108
	7.6	7.77	138	422	32.8	9,690	97	120
	13.9	5.99	129	446	28.9	9,060	96	120
	22.7	5.92	134	412	32.6	9,810	96	126
M.S.	Control	1.85	119	708	16.6	5,540	92	81
39	4.4	1.72	134	501	26.9	8,680	101	105
	7.2	1.74	129	517	25.0	8,230	99	104
	13.1	2.03	129	505	25.5	7,960	94	111
	21.4	4.52	128	517	24.7	8,040	94	121
B.B.	Control	1.35	96.8	499	19.4	6,810	89	92
54	2.7	1.03	91.0	421	21.6	7,780	86	96
	4.1	1.07	100	426	23.5	7,590	85	95
	6.7	0.97	94.7	386	24.5	8,260	84	97
	12.4	0.96	101	378	26.7	8,770	87	113
M.W.	Control	3.58	152	688	22.1	6,560	102	96
30	3.9	2.82	143	605	23.6	6,680	95	128
	6.4	3.05	140	444	31.6	7,870	82	129
	11.7	4.53	162	497	32.5	6,660	78	144
	19.2	3.60	135	408	33.1	7,100	69	154
			Hypertensive patients					
C.H.	Control	1.27	114	478	23.9	9,380	107	92
43	3.0	1.58	125	478	26.4	8,110	94	96
	4.9	2.50	124	431	28.8	9,420	98	102
	9.0	1.79	117	391	29.8	11,000	103	104
	14.6	1.61	126	348	36.2	12,900	107	115
R.M.	Control	1.42	122	589	20.6	6,450	100	78
63	4.1	1.66	108	418	25.8	9,170	101	87
	12.2	0.99	92.0	336	27.4	10,600	109	123
	19.9	0.68	93.3	294	31.8	14,900	114	126
L.G.	Control	0.65	83.0	420	19.8	10,300	111	84
54	3.5	0.76	98.0	377	26.0	11,100	101	82
	5.7	0.55	88.3	308	28.6	13,100	104	84
	10.6	0.51	73.4	280	27.2	15,800	109	103
	17.2	0.55	83.7	274	30.6	18,000	122	112
L.C.	Control	1.24	110	568	19.4	7,770	107	74
42	6.2	1.22	110	420	26.2	9,400	97	90
	11.4	1.09	100	372	26.9	12,300	111	105
N.F.	Control	3.58	132	614	21.5	6,710	104	82
38	1.9	5.70	142	601	23.6	6,780	103	93
	3.9	5.58	139	518	26.8	8,210	107	109
	5.6	3.60	138	536	25.8	8,740	117	122
	9.3	3.02	120	387	31.0	13,400	128	147

* Clearance values are corrected to 1.73 m² body surface area. See Methods section for abbreviations.
† Subjects J.B. and J.M. are males.

TABLE II—(*Continued*)

Subject† Age	Epinephrine	Urine volume	GFR	RPF	FF	RR	P_m	Pulse
yrs	*μg/min/ 1.73 m²*	*ml/min*	*ml/min*	*ml/min*	*%*	*dynes-sec-cm⁻⁵*	*mm Hg*	*rate/min*
M.R.	Control	14.4	135	683	19.7	6,430	110	84
26	5.5	10.7	133	555	24.0	7,430	104	92
	11.5	6.28	131	490	26.7	8,060	100	104
	16.4	4.71	126	467	27.0	8,260	98	111
	21.9	6.87	137	427	32.1	9,150	99	116
	27.4	8.32	134	411	32.7	9,500	99	120
J.B.	Control	1.02	97.3	582	16.7	7,010	103	80
49	4.2	1.63	100	525	18.8	7,770	103	96
	10.5	2.23	114	444	25.7	8,500	96	108
	14.7	3.13	81.1	287	28.3	10,400	78	126
J.M.	Control	0.58	112	467	24.2	8,840	104	84
37	4.4	0.58	121	457	26.5	8,170	95	95
	10.9	0.93	120	388	31.0	9,489	94	107
	15.2	1.64	121	366	33.1	10,200	95	114
	21.8	1.45	124	348	35.6	10,500	93	124
L.L.	Control	7.39	115	580	19.9	7,770	113	84
39	4.5	5.62	106	455	23.3	9,150	105	88
	11.4	5.84	111	476	23.3	8,650	104	104
	15.9	1.70	96.9	393	24.6	10,300	102	110
P.T.	Control	0.89	143	623	23.0	6,970	109	84
42	3.8	1.22	143	568	25.2	7,180	103	99
	9.8	5.12	149	538	27.7	7,480	102	115
	13.5	13.0	142	487	29.1	8,380	103	122

early stages of their disease, as judged by the absence of proteinuria and by minimal retinal and cardiac abnormalities.

The effect of *l*-norepinephrine on systemic blood pressure and renal hemodynamics was examined in 13 normotensive and 7 hypertensive subjects, and of epinephrine in 5 normotensive and 10 hypertensive subjects on a regular diet with normal salt content (10 to 15 g sodium chloride per day). The effect of *l*-norepinephrine during restricted dietary intake of salt (250 mg sodium chloride per day) was examined in 3 of the normotensive and 3 of the hypertensive subjects and of epinephrine in 4 of the normotensive and 5 of the hypertensive subjects. Adherence to the regimen was verified by measurement of 24-hour urinary sodium excretion rates.

Fluids were withheld for 12 hours preceding the test, which was performed in the morning with the patient in the fasting state. Urine was collected from an indwelling catheter and the bladder was emptied by means of air and without washout. Surgical sterility was maintained throughout the test, and an antibiotic was administered for 5 days following the test.

After the injection of suitable priming doses of inulin and *p*-aminohippurate, a sustaining infusion of these substances dissolved in normal saline was administered at a rate of 2 ml per minute. Urine was collected during one to three periods totalling 30 to 45 minutes for the determination of glomerular filtration rate (GFR) and renal plasma flow (RPF). Thereafter an infusion of *l*-norepinephrine or epinephrine in concentrations of 1.5 μg per ml in 5 per cent dextrose in distilled water was administered at successively increasing rates, starting at approximately 2.5 μg per minute. In most of the normotensive subjects the dosage of *l*-norepinephrine or epinephrine was increased to approximately 30 μg per minute, but in hypertensive subjects adverse manifestations such as substernal pressure, throbbing headache, palpitation or cardiac arrhythmia precluded administration of doses much in excess of 10 μg per minute. A separate urine collection was made to correspond with each dosage of vasoconstrictor. At appropriate time intervals blood samples were drawn from an antecubital vein, centrifuged immediately, and the plasma stored in stoppered tubes. Systemic blood pressures were recorded every 3 to 5 minutes throughout the study by the auscultatory method and averaged for each period. The mean blood pressure (P_m) was calculated as one-third of pulse pressure plus the diastolic pressure. Renal resistance (RR) was calculated according to the method of Gomez (24). Inulin was determined by a modification of Harrison's method, and *p*-aminohippurate by the method of Smith (25). Urinary sodium concentrations were measured with a flame photometer using lithium as an internal standard.

The observed values for GFR, RPF, P_m and RR in each subject were plotted against dosage of vasoconstrictor and the values for doses of 2.5, 5.0, 7.5, and 10 μg per minute were then derived for each parameter by interpolation. Mean values for both actual and percentage change were calculated from the interpolated values for the observations made during normal salt intake. Mean values were not calculated for the stud-

TABLE III

Summary of effects of l-norepinephrine and epinephrine in normotensive and hypertensive subjects on regular salt intake *

Subjects	No.	Mean pressure			Renal plasma flow			Renal resistance			Glomerular filtration rate				Filtration fraction			
		Control	Response		Control	Response		Control	Response		Control	Response			Control	Response		
			Actual	Δ†		Actual	Δ		Actual	Δ		Actual	Δ			Actual	Δ	
		mm Hg	*mm Hg*	*mm Hg*	*ml/ min*	*ml/ min*	*ml/ min*	*dynes-sec-cm⁻⁵*	*dynes-sec-cm⁻⁵*	*dynes-sec-cm⁻⁵*	*ml/ min*	*ml/ min*	*ml/ min*	%				%
								l-Norepinephrine										
Normotensive	13	86	108	+22	708	551	−157	4,830	8,110	+3,280	133	133	0	0.0	0.191	0.242	+0.051	+28.2
Hypertensive	7	116	145	+29	504	409	− 95	9,660	14,400	+4,740	110	117	+7	+3.48	0.221	0.273	+0.052	+24.7
								Epinephrine										
Normotensive	5	94	88	− 6	616	467	−149	6,360	7,820	+1,460	120	128	+8	+6.60	0.196	0.262	+0.066	+35.1
Hypertensive	10	107	105	− 2	569	412	−157	7,770	10,300	+2,530	116	114	−2	−2.92	0.209	0.276	+0.067	+32.7

* Response recorded at dosage of 10 μg/min/1.73m². All values represent means.
† Δ = change from control.

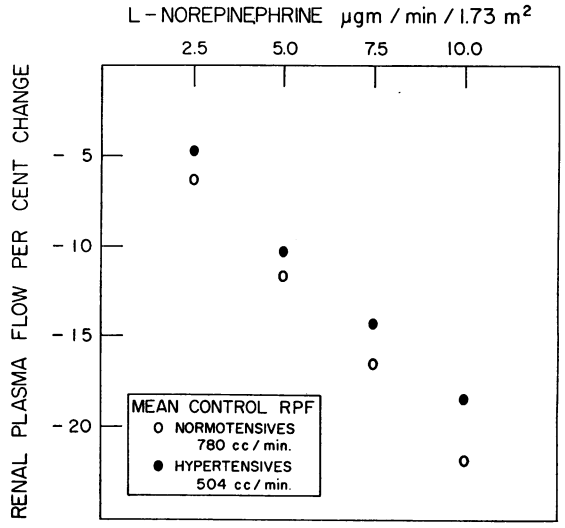

FIG. 1. EFFECT OF *l*-NOREPINEPHRINE ON RENAL PLASMA FLOW. Each open circle represents the mean value for 13 normotensive subjects and each closed circle the mean for 7 hypertensive subjects.

ies performed during restricted dietary intake of salt because of the small number of subjects.

The observed values for all doses administered are presented in Tables I, II, IV and V. However, for the purpose of comparing the responses in hypertensive and normotensive subjects we have utilized the values inter-

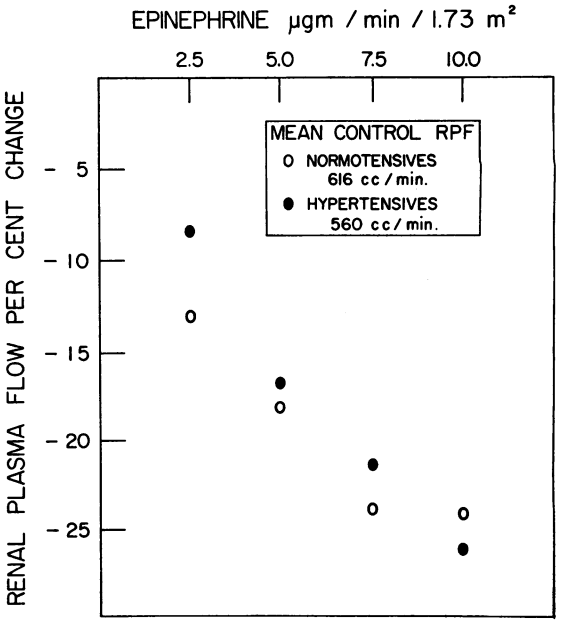

FIG. 2. EFFECT OF EPINEPHRINE ON RENAL PLASMA FLOW. Each open circle represents the mean value for 5 normotensive subjects and each closed circle the mean for 10 hypertensive subjects.

polated at 10 μg per minute (Figures 1–5 and Tables III, VI and VII) and will refer to these in our results, inasmuch as this is the largest dose at which data are available for comparison in all subjects.

RESULTS

Regular diet with normal salt content (Tables I, II, and III; Figures 1–5). *l*-Norepinephrine induced a mean decrease in RPF of 157 ml per minute (− 21.8 per cent) in 13 normotensive subjects and of 95 ml per minute (− 18.1 per cent) in 7 hypertensive subjects. Epinephrine induced a

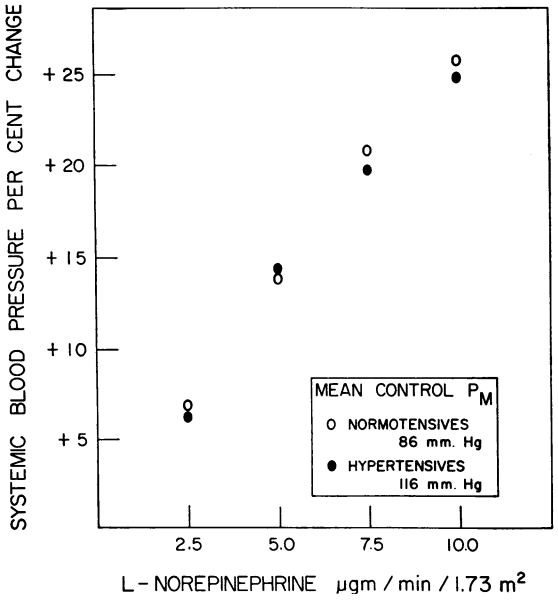

FIG. 3. EFFECT OF *l*-NOREPINEPHRINE ON SYSTEMIC BLOOD PRESSURE. Each open circle represents the mean value for 13 normotensive subjects and each closed circle the mean for 7 hypertensive subjects.

mean decrease in RPF of 149 ml per minute (− 23.8 per cent) in 5 normotensive subjects and of 157 ml per minute (− 26.0 per cent) in 10 hypertensive subjects.

l-Norepinephrine caused comparable increases in P_m in the two groups, a mean of 22 mm Hg (+ 25.6 per cent) in normotensives and 29 mm Hg (+ 24.7 per cent) in hypertensives. Epinephrine caused no significant changes in P_m in either normotensives or hypertensives, a mean of −6 mm Hg (− 5.7 per cent) in the former and − 2 mm Hg (− 1.54 per cent) in the latter.

l-Norepinephrine did not change GFR in either group. Since percentage decrease in RPF was

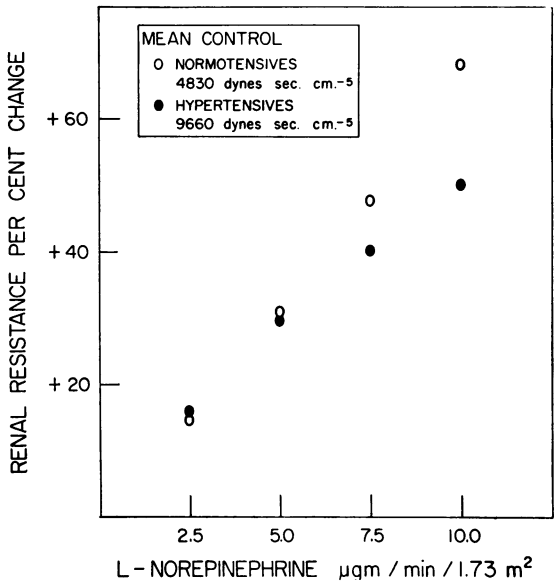

FIG. 4. EFFECT OF *l*-NOREPINEHRINE ON RENAL RESISTANCE. Each open circle represents the mean value for 13 normotensive subjects and each closed circle the mean for 7 hypertensive subjects.

comparable in normotensive and hypertensive subjects, percentage increases in filtration fraction (FF) were also equal, in the former from a mean control value of 0.191 to 0.244 (+ 29.2 per cent) and in the latter from 0.221 to 0.273 (+ 33.1 per cent). Similarly, epinephrine failed to affect GFR, and FF was increased to the same extent in normotensive and hypertensive subjects, from 0.196 to 0.262 (+ 35.1 per cent) in the former and from 0.209 to 0.276 (+ 32.7 per cent) in the latter.

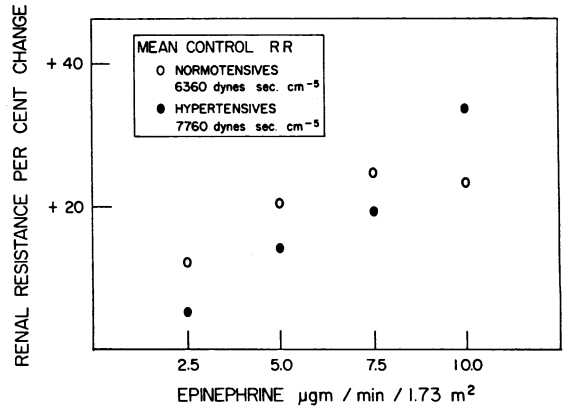

FIG. 5. EFFECT OF EPINEPHRINE ON RENAL RESISTANCE. Each open circle represents the mean value for 5 normotensive subjects and each closed circle the mean for 10 hypertensive subjects.

TABLE IV

Effect of l-norepinephrine on renal and systemic hemodynamics in normotensive and hypertensive subjects on reduced salt intake *

Subject† Age	*l*-Norepinephrine	Urine volume	GFR	RPF	FF	RR	P_m	Pulse
yrs	*μg/min/1.73 m²*	*ml/min*	*ml/min*	*ml/min*	*%*	*dynes-sec-cm⁻⁵*	*mm Hg*	*rate/min*
			Normotensive subjects					
A.B.	Control	1.51	108	755	14.4	4,130	84	111
19	4.7	1.23	96.3	514	18.7	7,530	102	73
	7.6	1.78	105	481	21.9	8,340	105	67
	14.0	1.10	84.1	302	28.0	14,000	110	62
	22.8	1.39	86.2	258	33.4	17,700	118	61
M.So.	Control	2.56	118	694	17.1	4,990	89	100
45	4.6	2.13	114	535	21.3	7,620	103	95
	7.6	1.98	104	416	25.0	10,700	112	92
	13.9	1.27	89	324	27.3	14,900	120	81
	22.5	0.85	78	236	32.9	21,700	127	73
M.S.	Control	2.84	83.6	602	20.1	4,810	75	90
39	2.9	0.89	111	527	21.0	6,090	82	76
	3.4	2.63	112	465	24.2	7,480	88	77
	7.2	3.61	124	464	26.8	8,180	95	76
	13.1	5.88	113	315	35.8	13,600	106	74
	21.4	6.25	101	314	32.2	14,500	112	77
O.V.	Control	1.15	122	788	15.6	3,560	79	84
35	4.1	0.73	101	597	16.9	4,760	80	74
	6.7	0.98	107	588	18.2	5,170	85	76
	12.4	0.61	116	563	20.6	5,700	89	75
	20.0	0.52	116	537	21.6	6,500	96	67
			Hypertensive patients					
E.H.	Control	0.39	96.0	382	25.1	10,300	100	66
42	1.2	0.40	89.4	390	22.9	11,100	109	56
	3.7	0.39	88.5	350	25.8	15,000	130	58
	11.1	0.48	96.6	299	32.4	19,900	146	56
L.C.	Control	1.42	66.2	420	15.8	10,000	106	84
31	7.4	2.44	85.8	439	19.5	12,100	131	76
	13.8	2.07	75.7	376	20.2	14,300	133	63
	22.3	1.48	93.0	339	27.5	16,400	137	57
M.L.	Control	0.37	97.0	459	21.2	8,250	98	69
26	5.4	0.60	107	386	27.7	12,300	120	64
	12.5	2.39	105	318	32.0	15,800	127	63
	20.4	1.97	99.0	284	34.9	19,500	139	57

* Clearance values are corrected to 1.73 m² body surface area. See Methods section for abbreviations.
† All subjects are females.

l-Norepinephrine induced a mean increase in RR of 3,280 dynes-sec-cm^{-5} (+ 68.5 per cent) in normotensive and of 4,740 dynes-sec-cm^{-5} (+ 50.3 per cent) in hypertensive subjects. Similarly, epinephrine induced equal response in normotensive and hypertensive subjects, 1,460 dynes-sec-cm^{-5} (+ 23.7 per cent) in the former and 2,530 dynes-sec-cm^{-5} (+ 33.9 per cent) in the latter.

Regular diet with reduced salt content (Tables IV–VII). In four normotensive subjects salt restriction for periods of 17 to 45 days did not affect control values for P_m, RPF or RR in a significant or consistent manner. However, in some hypertensive subjects salt restriction for periods of 8 to 18 days did affect systemic and renal hemodynamics: systemic pressure decreased in three of eight, RPF decreased in six of eight, and RR increased in four of the eight hypertensive subjects.

Dietary salt restriction did not alter the response of P_m to *l*-norepinephrine in the normotensive group: P_m increased 27 per cent on salt restriction as compared with 21 per cent on regular salt intake in Patient A.B.; 29 as compared

TABLE V

Effect of epinephrine on renal and systemic hemodynamics in normotensive and hypertensive subjects on reduced salt intake *

Subject† Age	Epinephrine	Urine volume	GFR	RPF	FF	RR	P_m	Pulse
yrs	*μg/min/ 1.73 m²*	*ml/min*	*ml/min*	*ml/min*	*%*	*dynes-sec-cm⁻⁵*	*mm Hg*	*rate/min*
			Normotensive subjects					
A.B.	Control	4.23	111	749	15.0	4,270	83	100
19	4.7	2.65	112	607	18.5	4,760	76	131
	7.6	4.75	114	590	19.4	4,610	72	136
	14.0	8.77	108	498	21.6	5,540	73	141
	22.8	8.05	101	488	20.8	5,660	73	140
M.So.	Control	0.56	108	553	19.5	6,120	87	96
45	3.2	0.51	102	488	20.9	6,560	83	101
	4.6	0.49	108	424	25.5	7,940	83	114
	7.6	0.43	110	408	27.0	8,810	84	118
	13.9	0.89	112	382	29.3	8,650	84	121
	22.6	2.01	117	360	32.5	9,670	88	126
M.S.	Control	0.70	118	500	23.6	6,240	81	104
39	3.0	1.77	123	546	22.6	5,700	81	105
	4.4	5.47	128	506	25.3	5,900	78	104
	7.2	3.25	130	463	28.1	7,320	80	103
	13.1	3.02	135	447	30.2	7,180	83	108
	21.4	1.90	110	330	33 3	10,000	85	114
B.B.	Control	0.95	78.4	524	15.0	6,670	85	88
54	2.7	1.00	81.0	550	14.7	6,100	82	91
	4.1	1.18	80.9	445	18.2	7,750	84	96
	6.7	1.00	79.9	476	16.8	7,340	86	103
	12.4	0.82	82.0	445	18.4	7,220	79	108
	20.2	1.30	95.0	493	19.3	6,710	81	117
			Hypertensive patients					
E.H.	Control	5.52	77.2	396	19.5	10,600	106	75
42	2.4	6.38	85.2	431	19.8	10,100	109	74
	6.1	7.77	91.4	408	22.4	9,000	94	88
	11.1	7.82	87.1	378	23.0	9,610	93	94
	18.2	8.80	96.0	382	25.1	9,970	97	105
M.L.	Control	0.36	109	431	25.2	8,550	97	73
26	3.5	0.38	115	415	27.6	8,660	94	93
	6.8	0.49	140	457	30.5	8,050	97	101
	12.5	0.33	120	313	38.3	14,600	118	135
	20.4	0.69	129	299	43.3	14,700	114	133
M.R.	Control	8.70	146	695	21.2	4,670	85	91
26	4.6	7.52	138	623	22.2	4,930	80	100
	15.0	4.82	129	460	28.1	6,770	81	109
	16.1	3.14	124	382	32.3	8,720	86	115
	23.0	1.72	135	376	35.9	8,850	86	118
	27.6	1.60	133	344	38.7	10,300	91	124
N.F.	Control	4.30	109	579	18.9	6,210	101	92
39	3.9	4.03	123	561	21.9	6,960	99	100
	9.8	3.72	101	389	26.0	10,600	104	113
	13.7	2.63	102	380	26.8	11,300	108	120
	19.5	1.30	71.8	255	28.2	15,800	102	125
J.M.	Control	0.53	102	411	24.8	10,000	104	88
37	4.4	0.73	112	434	25.8	9,600	105	99
	10.9	0.77	87.9	320	27.4	13,200	106	114
	15.2	0.61	83.3	288	28.9	14,400	104	124
L.L.	Control	3.16	95.9	659	14.5	6,450	107	98
39	4.5	5.19	104	606	17.2	6,660	102	104
	11.4	2.44	91.2	498	18.3	7,300	93	120
	15.9	1.16	95.5	525	18.2	7,100	95	125
P.T.	Control	0.40	108	496	22.7	9,000	112	82
42	3.8	6.38	121	507	23.8	8,480	108	100
	9.6	8.54	107	416	25.7	9,800	103	109
	13.5	7.14	106	417	25.4	9,460	100	121

* Clearance values are corrected to 1.73 m² body surface area. See Methods section for abbreviations.
† J.M. is the only male subject.

TABLE VI

Effect of reduced salt intake on the response to l-norepinephrine in normotensive and hypertensive subjects *

Subjects	Mean pressure			Renal plasma flow			Renal resistance			Glomerular filtration rate		
	Control	Response		Control	Response		Control	Reponse		Control	Response	
		Δ	Δ		Δ	Δ		Δ	Δ		Δ	Δ
	mm Hg	*mm Hg*	%	*ml/min*	*ml/min*	%	*dynes-sec-cm⁻⁵*	*dynes-sec-cm⁻⁵*	%	*ml/min*	*ml/min*	%
Normotensive subjects												
A.B.												
Ward	86	+18	+21.0	709	−174	−24.6	4,500	+3,100	+ 69.0	118	− 2	− 1.69
S.R. [19]†	84	+23	+27.0	755	−335	−44.4	4,130	+6,730	+154.0	108	−10	− 9.25
M.So.												
Ward	79	+30	+38.0	604	−148	−2 5	5,560	+5,190	+ 48.2	118	0	0
S.R. [17]	89	+26	+29.0	694	−307	− .3	4,990	+7,210	+145.0	118	−20	−17.0
M.Sp.												
Ward	77	+25	+32.0	602	− 70	−11.6	5,070	+2,530	+ 50.0	122	+ 3	+ 2.46
S.R. [21]	75	+25	+33.0	602	−207	− 34.4	4,810	+5,790	+120.0	87.6	+35	+41.8
Hypertensive patients												
E.H.												
Ward	109	+30	+27.5	567	−113	−19.9	7,650	+4,850	+ 38.8	129	+ 5	+ 3.88
S.R. [18]	100	+46	+46.0	382	− 77	−20.1	10,300	+8,800	+ 85.4	96.0	− 0.5	− 0.52
L.C.												
Ward	111	+24	+21.6	583	−184	−31.6	7,600	+5,500	+ 72.3	94.5	− 1.5	− 1.58
S.R. [14]	106	+26	+24.5	420	− 10	− 2.4	10,000	+3,000	+ 30.0	66.2	+15.3	+23.1
M.L.												
Ward	113	+17	+15.0	531	− 85	−16.0	8,500	+3,250	+ 38.2	115	+ 3	+ 2.60
S.R. [11]	98	+26	+26.6	459	−117	−25.5	8,250	+6,450	+ 78.2	97.0	+ 9	+ 9.28

* Clearance values are corrected to 1.73 m² body surface area. Response recorded at dosage of 10 μg/min/1.73 m². Δ = change from control.
† Number of days on reduced salt intake in brackets. Ward = regular diet; S.R. = salt-restricted diet.

TABLE VII

Effect of reduced salt intake on the response to epinephrine in normotensive and hypertensive subjects *

Subjects	Mean pressure			Renal plasma flow			Renal resistance			Glomerular filtration rate		
	Control	Response		Control	Response		Control	Response		Control	Response	
		Actual Δ	Δ		Actual Δ	Δ		Actual Δ	Δ		Actual Δ	Δ
	mm Hg	*mm Hg*	%	*ml/min*	*ml/min*	%	*dynes-sec-cm⁻⁵*	*dynes-sec-cm⁻⁵*	%	*ml/min*	*ml/min*	%
Normotensive subjects												
A.B.												
Ward	83	0	0	655	−120	−18.3	4,880	+ 950	+ 19.9	104	+18	+17.3
S.R. [25]†	83	−11	−13.2	749	−197	−26.3	4,270	+ 630	+ 14.7	111	+ 1	+ 0.9
M.So.												
Ward	102	− 5	− 4.90	531	−101	−19.0	8,000	+1,370	+ 17.2	128	+ 7	+ 5.47
S.R. [26]	87	− 2	− 2.30	553	−155	−28.0	6,120	+2,630	+ 43.0	108	+ 3	+ 2.78
M.Sp.												
Ward	92	+ 5	+ 3.26	708	−198	−28.0	5,540	+2,560	+ 46.3	119	+10	+ 8.40
S.R. [26]	81	0	0	500	− 47	− 9.41	6,240	+1,010	+ 16.2	118	+14	+11.8
B.B.												
Ward	89	− 5	− 5.63	499	−117	−23.5	6,810	+1,940	+ 28.5	96.8	+ 1.2	+ 1.24
S.R. [45]	85	− 3	− 3.53	524	− 69	−13.2	6,670	+ 630	+ 11.1	78.4	+ 2.6	+ 3.32
Hypertensive patients												
M.R.												
Ward	110	−10	− 9.10	683	−175	−25.6	6,430	+1,420	+ 20.8	135	− 4.0	− 2.96
S.R.[16]	84	− 3	− 3.57	695	−154	−22.2	4,670	+1,580	+ 33.8	146	−12.0	− 8.22
N.F.												
Ward	104	+27	+26.0	614	−250	−40.7	6,710	+6,790	+101.0	132	−14.0	−10.6
S.R. [11]‡	101	+ 3	+ 2.97	579	−199	−34.4	6,210	+4,390	+ 70.7	109	− 8.0	− 7.33
J.M.												
Ward	104	−11	−11.8	467	− 72	−15.4	8,840	+ 340	+ 4.07	112	+ 8.0	+ 7.14
S.R. [8]‡	104	+ 2	+ 1.92	411	− 76	−18.5	10,000	+2,700	+ 27.0	102	−10.0	− 9.80
L.L.												
Ward	113	− 9	− 8.85	580	−110	−19.0	7,770	+ 980	+ 12.6	115	− 5.0	− 4.34
S.R. [8]‡	107	+11	+10.3	659	−143	−21.7	6,450	+ 800	+ 12.4	95.9	− 1.9	− 1.98
P.T.												
Ward	109	− 7	− 6.43	623	− 93	−15.0	6,970	+ 530	+ 7.61	143	+ 5.0	+ 3.49
S.R. [9]‡	112	− 9	− 8.03	496	− 80	−16.2	9,000	+ 800	+ 8.88	108	− 1.0	− 0.925

* Clearance values are corrected to 1.73 m² body surface area. Response recorded at dosage of 10 μg/min/1.73 m². Δ = change from control.
† Number of days on reduced salt intake in brackets.
‡ Chlorothiazide, 1 g/day on the first 3 days of reduced salt intake.

with 38 per cent in M.So.; and 33 as compared with 32 per cent in M.Sp. Salt restriction, however, increased P_m responses to *l*-norepinephrine in two of three hypertensive patients, 46 per cent as compared with 27.5 per cent in Patient E.H., 26.6 as compared with 15.0 per cent in M.L., and 24.5 as compared with 21.6 per cent in L.C. Salt restriction did not affect the response in P_m to epinephrine in either normotensive or hypertensive subjects.

Salt restriction exaggerated the response of RPF to *l*-norepinephrine in normotensive subjects: RPF decreased 44.4 per cent as compared with 24.6 per cent on regular salt intake in Patient A.B.; 44.3 as compared with 24.5 per cent in M.So.; and 34.4 as compared with 11.6 per cent in M.Sp. Salt restriction had no consistent effect on response of RPF to *l*-norepinephrine in hypertensive subjects. The response of RPF to epinephrine was not affected by sodium restriction in either normotensive or hypertensive subjects.

Salt restriction exaggerated the effect of *l*-norepinephrine on RR in normotensive subjects. RR increased 154 per cent on sodium restriction as compared with 69 per cent on regular salt intake in Patient A.B., 145 as compared with 48.2 per cent in M.So., and 120 as compared with 50 per cent in M.Sp. In two of the three hypertensive patients, salt restriction increased the effect of *l*-norepinephrine on RR; this increased response in RR resulted from greater increase in P_m rather than from decrease in RPF. Salt restriction had no consistent effect on the response of RR to epinephrine in either normotensive or hypertensive subjects.

DISCUSSION

Our data demonstrate that the renal vasoconstrictor response to *l*-norepinephrine and epinephrine, measured as per cent change in renal resistance, is the same in normotensive and hypertensive subjects. Comparison of arteriolar reactivity in normotensive and hypertensive subjects necessitates interpreting changes produced in the resistance of arterioles that differ in initial circumference and initial degree of vasoconstriction, and that differ structurally as regards smooth muscle mass and sclerosis.

A given decrease in vessel circumference will result in a greater decrease in cross-sectional area (or increase in resistance) in a smaller (hypertensive) vessel than in a larger (normotensive) one. This disproportionate effect on renal resistance of given amounts of arteriolar muscle shortening may best be taken into account by comparing percentage rather than absolute changes in renal resistance. The proportional increases in renal resistance observed in the two groups in response to *l*-norepinephrine and epinephrine indicate that the actual circumference of the renal arterioles decreased to a greater extent in normotensive subjects, despite the fact that the absolute increase in renal resistance was greater in hypertensive patients.

The percentile method of comparison also takes into account the fact that the initial degree of preexisting vasoconstriction affects arteriolar reactivity; i.e., a less constricted vessel would be expected to respond by greater shortening than the more constricted vessel. Although Folkow and Öberg (26) reported that percentage increase in flow resistance in the hind limb of a cat is less in constricted vessels than in normal or dilated ones in response to norepinephrine or angiotensin, we doubt that data obtained in anesthetized cats, in which variations in initial vascular tone were induced by bilateral carotid artery occlusion or vagal stimulation, can be used to interpret relative reactivity in normotensive and hypertensive man.

The muscle mass of the renal vasculature might also affect comparison of reactivity to vasoconstrictor agents. It would seem reasonable to expect that a vessel with hypertrophied muscle fibers would respond with greater constriction even though reactivity of individual muscle fibers was not greater than normal. The failure of hypertensive patients to respond to a greater extent than do normotensive subjects, despite the presence of muscular hypertrophy in the former, supports the interpretation that reactivity to *l*-norepinephrine and epinephrine is not increased in hypertension.

The increased initial renal resistance in hypertensive subjects may be attributed to functional arteriolar constriction, anatomical narrowing, or both. Sclerotic changes in the vessel wall might

decrease contractility and in this way interfere with the action of a vasoconstrictor agent. However, our studies are not significantly affected by such changes in the vessel wall, since patients were selected early in the course of hypertensive disease (as judged by history, clinical data, and the presence of only minimal reductions in RPF), indicating that functional vasoconstriction was predominantly responsible for the increased renal resistance.

A maximal limit to vasoconstriction in hypertensive patients might limit reactivity and in this way affect the comparison with normotensive subjects. The similarity of the curves for percentage change in renal resistance (Figures 4 and 5) throughout the dosage range of vasoconstrictors administered demonstrates that comparison of reactivity in normotensive and hypertensive subjects is not affected by such a ceiling.

Renal arteriolar reactivity to vasoconstrictor stimuli would be more profitably studied by employing an agent whose action is limited to the renal vascular bed. *l*-Norepinephrine increased systemic resistance and pressure in addition to its direct effect on the renal circulation and these systemic changes of themselves may induce renal vasoconstriction. However, unless the effect on the renal circulation of comparable changes in systemic pressure differs in normotensive and hypertensive subjects, the possible influence of systemic pressure on renal resistance should not limit the comparison of renal arteriolar reactivity in the two groups. Epinephrine did not affect mean systemic pressure, and here the changes in renal resistance may be interpreted unequivocally as reflecting the direct effect of the vasoconstrictor agent on the renal vessels.

Assuming that cardiac output is affected similarly in the hypertensive and normotensive subjects by both epinephrine and *l*-norepinephrine, as has been reported by Goldenberg and associates (8), our observations indicate that the reactivity of the systemic vessels to epinephrine and *l*-norepinephrine is the same in normotensive and hypertensive subjects, since relative changes in systemic pressure were equal in both groups. The observation that reactivity of the systemic arterioles is comparable in normotensive and hypertensive subjects does not support the thesis that essential hypertension is related to increased vascular sensitivity to circulating norepinephrine.

Confirming the observations of others (27–29), sodium restriction for periods ranging from 1 to 4 weeks produced a decrease in both systemic pressure and renal plasma flow in hypertensive patients; these did not decrease in the normotensive subjects. Sodium restriction causes reduction in extracellular fluid and plasma volumes (28, 30–32), and in cardiac output (31, 32). These hemodynamic effects could account for the decreases in systemic pressure and renal plasma flow observed in the hypertensive patients. Decrease of renal plasma flow in hypertensive patients indicates that greater renal vasoconstriction occurred in the hypertensive than in the normotensive subjects, and may be explained by a difference in renal response to systemic changes induced by sodium restriction or may indicate that greater reductions in extracellular fluid volume and cardiac output occurred in hypertensive subjects. Our observation that sodium restriction produced greater weight loss in hypertensive than in normotensive subjects supports the latter possibility.

Restriction of sodium intake failed to decrease renal arteriolar reactivity to *l*-norepinephrine or epinephrine in both normotensive and hypertensive subjects. In fact, the response to *l*-norepinephrine was enhanced in both groups, the effect being relatively greater in normotensive than in hypertensive subjects. This enhanced renal vasoconstrictor response is unexplained, but may reflect differences in smooth muscle contractility associated with changes in sodium content or increased sensitivity to vasoconstrictor influences resulting from reduced circulating blood volume. Tobian and Fox (33) have reported that there is a gain of sodium and a loss of potassium in the arterial wall in dogs during norepinephrine infusion and have suggested that these electrolyte shifts play a part in smooth muscle contractility. Friedman, Jamieson and Friedman (34) have demonstrated that smooth muscle tone and responsiveness to drug-induced contraction are enhanced in the rat when the ratio of extracellular to intracellular sodium concentration is reduced. The applicability of these observations to our results cannot be assessed inasmuch as we have no data relative to the effect of sodium restriction on the

sodium gradient across the vessel wall in our patients. The fact that the reactivity of the renal circulation to *l*-norepinephrine was increased to a greater extent in normotensive than in hypertensive subjects during sodium restriction may be attributed to the initially greater vasoconstriction which had already been produced by sodium restriction in the latter.

CONCLUSIONS

1. Renal and systemic arteriolar vasoconstrictor reactivity is equal in normotensive and hypertensive subjects, as shown by equal relative increases in both renal resistance and systemic blood pressure in response to the administration of *l*-norepinephrine and epinephrine. This observation is contrary to the thesis that essential hypertension is related to increased vascular sensitivity to circulating norepinephrine.

2. Restricted sodium intake fails to decrease renal arteriolar vasoconstrictor reactivity to *l*-norepinephrine and epinephrine in either normotensive or hypertensive subjects.

REFERENCES

1. Kylin, E. Über Hypertonie und Nierenkrankheit. Zbl. inn. Med. 1921, **42**, 441.
2. Brems, A. Über die perorale Adrenalinblutdruckwirkung. Acta med. scand. 1926, **64**, 69.
3. Gordon, W., and Levitt, G. Blood pressure changes in normals and in hypertensives after intravenous epinephrine and histamine. J. clin. Invest. 1935, **14**, 367.
4. Fatherree, T. J., and Hines, E. A., Jr. The blood pressure response to epinephrine administered intravenously to subjects with normal blood pressure and to patients with essential hypertension. Amer. Heart J. 1938, **16**, 66.
5. Judson, W. E., Culbertson, J. W., Tinsley, C. M., Litter, J., and Wilkins, R. W. The comparative effects of small intravenous doses of epinephrine upon arterial pressure and pulse rate in normotensive subjects and in hypertensive patients before and after thoracolumbar sympathectomy. J. clin. Invest. 1950, **29**, 1405.
6. Judson, W. E., Epstein, F. H., and Wilkins, R. W. The comparative effect of small intravenous doses of *l*-norepinephrine upon arterial pressure and pulse rate in normotensive subjects and hypertensive patients before and after thoracolumbar sympathectomy. J. clin. Invest. 1950, **29**, 1414.
7. Barany, F. R., and James, P. The sensitivity to *l*-noradrenalin of patients with high blood pressure. Clin. Sci. 1959, **18**, 543.
8. Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, D. G., and Roh, C. E. The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. Amer. J. Med. 1948, **5**, 792.
9. Clough, P. W. A study of the cardiovascular reaction to epinephrin. Epinephrin sensitiveness in patients with hypertension. Bull. Johns Hopk. Hosp. 1920, **31**, 266.
10. Jensen, J. The adrenalin test in hypertension. Amer. Heart J. 1930, **5**, 763.
11. Doyle, A. E., and Black, H. Reactivity to pressor agents in hypertension. Circulation 1955, **12**, 974.
12. Pickering, G. W., and Kissin, M. The effects of adrenaline and of cold on the blood pressure in human hypertension. Clin. Sci. 1936, **2**, 201.
13. Prinzmetal, M., and Wilson, C. The nature of the peripheral resistance in arterial hypertension with special reference to the vasomotor system. J. clin. Invest. 1936, **15**, 63.
14. Mendlowitz, M., and Naftchi, N. Work of digital vasoconstriction produced by infused norepinephrine in primary hypertension. J. appl. Physiol. 1958, **13**, 247.
15. Doyle, A. E., Fraser, J. R., and Marshall, R. J. Reactivity of forearm vessels to vasoconstrictor substances in hypertensive and normotensive subjects. Clin. Sci. 1959, **18**, 441.
16. Duff, R. S. Adrenaline sensivity of peripheral blood vessels in human hypertension. Brit. Heart J. 1957, **19**, 45.
17. Greisman, S. E. The reaction of the capillary bed of the nailfold to the continuous intravenous infusion of levo-nor-epinephrine in patients with normal blood pressure and with essential hypertension. J. clin. Invest. 1954, **33**, 975.
18. Chasis, H., Ranges, H. A., Goldring, W., and Smith, H. W. The control of renal blood flow and glomerular filtration in normal man. J. clin. Invest. 1938, **17**, 683.
19. Smythe, C. McC., Nickel, J. F., and Bradley, S. E. The effect of epinephrine (USP), *l*-epinephrine and *l*-norepinephrine on glomerular filtration rate, renal plasma flow, and the urinary excretion of sodium, potassium, and water in normal man. J. clin. Invest. 1952, **31**, 499.
20. Pullman, T. N., and McClure, W. W. The response of the renal circulation in man to constant-speed infusion of *l*-norepinephrine. Circulation 1954, **9**, 600.
21. Raab, W., Humphreys, R. J., Makous, N., DeGrandpré, R., and Gigee, W. Pressor effects of epinephrine, norepinephrine and desoxycorticosterone acetate (DCA) weakened by sodium withdrawal. Circulation 1952, **6**, 373.
22. Aleksandrow, D., Wysznacka, W., and Gajewski, J. Influence of chlorothiazide upon arterial responsiveness to nor-epinephrine in hypertensive subjects. New Engl. J. Med. 1959, **261**, 1052.

23. Dahl, L. K. Pressor effects of norepinephrine after drastic reduction of sodium intake. Circulation 1957, **15**, 231.
24. Gomez, D. M. L'hémodynamique de la circulation renalé. Rev. Sci. 1947, **85**, 451.
25. Smith, H. W. Principles of Renal Physiology. New York, Oxford Univ. Press, 1956.
26. Folkow, B., and Öberg, B. The effect of functionally induced changes in wall/lumen ratio on the vasoconstrictor response to standard amounts of vasoactive agents. Acta physiol. scand. 1959, **47**, 131.
27. Chasis, H., Goldring, W., Breed, E. S., Schreiner, G. E., and Bolomey, A. A. Salt and protein restriction—Effects on blood pressure and renal hemodynamics in hypertensive patients. J. Amer. med. Ass. 1950, **142**, 711.
28. Weston, R. E., Hellman, L., Escher, D. J. W., Edelman, I. S., Grossman, J., and Leiter, L. Studies on the influence of the low sodium cardiac diet and the Kempner regimen on renal hemodynamics and electrolyte excretion in hypertensive subjects. J. clin. Invest. 1950, **29**, 639.
29. Corcoran, A. C., Taylor, R. D., and Page, I. H. Controlled observations on the effect of low sodium dietotherapy in essential hypertension. Circulation 1951, **3**, 1.
30. McCance, R. A. The effect of salt deficiency in man on the volume of the extracellular fluids, and on the composition of sweat, saliva, gastric juice and cerebrospinal fluid. J. Physiol. (Lond.) 1938, **92**, 208.
31. Dustan, H. P., Cumming, G. R., Corcoran, A. C., and Page, I. H. A mechanism of chlorothiazide-enhanced effectiveness of antihypertensive ganglioplegic drugs. Circulation 1959, **19**, 360.
32. Frohlich, E. D., Schnaper, H. W., Wilson, I. M., and Freis, E. D. Hemodynamic alterations in hypertensive patients due to chlorothiazide. New Engl. J. Med. 1960, **262**, 1261.
33. Tobian, L., and Fox, A. The effect of nor-epinephrine on the electrolyte composition of arterial smooth muscle. J. clin. Invest. 1956, **35**, 297.
34. Friedman, S. M., Jamieson, J. D., and Friedman, C. L. Sodium gradient, smooth muscle tone, and blood pressure regulation. Circulat. Res. 1959, **7**, 44.

ANNOUNCEMENT OF MEETINGS

The Nineteenth Annual Meeting of THE AMERICAN FEDERATION FOR CLINICAL RESEARCH will be held in Atlantic City, N. J., on Sunday, April 29, 1962 at 9:00 a.m. at the Casino Theatre on the Steel Pier. On Sunday afternoon, April 29, 1962, joint sectional meetings with The American Society for Clinical Investigation will be held in rooms in Chalfonte-Haddon Hall; and on Sunday evening, additional meetings will be held under the auspices of The American Federation for Clinical Research, in Chalfonte-Haddon Hall.

The Fifty-fourth Annual Meeting of THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, INC., will be held in Atlantic City, N. J., on Sunday afternoon, April 29, 1962, in Chalfonte-Haddon Hall in simultaneous programs sponsored in conjunction with The American Federation for Clinical Research; and on Monday, April 30, at 9:00 a.m. at the Casino Theatre on the Steel Pier.

THE ASSOCIATION OF AMERICAN PHYSICIANS will hold its Seventy-fifth Annual Meeting at Atlantic City, N. J., at the Casino Theatre on the Steel Pier on Tuesday, May 1, 1962, at 9:30 a.m., and in the Vernon Room, Chalfonte-Haddon Hall on Wednesday, May 2, 1962, at 9:30 a.m.