THE EFFECTS OF HISTAMINE ON RENAL FUNCTION IN HYPERTENSIVE AND NORMOTENSIVE SUBJECTS[1]

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(Received for publication June 16, 1948)

Little is known of the effects of histamine upon the renal circulation. According to Dale and Laidlaw (1), the rate of urine flow after the injection of histamine follows roughly the arterial blood pressure; their renal plethysmographic studies showed a decrease in the volume of the kidney, possibly due to active arteriolar constriction. These observations have generally been confirmed by other investigators (2–4), who found a reduced blood flow in laboratory animals and an oliguria in human beings. Following administration of histamine to human subjects, Bjering (5) noted a fall in the clearances of urea and creatinine which he ascribed to changes in renal circulation.

The favorable effect of antihistaminic drugs upon experimental nephritis in rabbits and on albuminuria and hematuria in certain cases of human glomerular nephritis suggests that histamine-like substances may cause the glomerular vasodilatation and increased permeability observed in the latter disease (6, 7). Some human subjects manifesting arterial hypertension of the "neurogenic" type (8) show a definite hypersensitivity to histamine and respond to the intracutaneous injection of a small dose with a so-called "diencephalic blush" (9). Because of these observations bearing on the influence of histamine upon renal and vascular disease, an attempt was made to investigate further the effect of histamine upon renal function. We describe below the influence of a subcutaneous injection of histamine upon renal function as measured by the clearance technique.

SUBJECTS AND METHODS

Experiments were performed upon five patients with essential hypertension without ascertainable antecedent renal disease, and upon five normotensive patients.

Mannitol and para-aminohippurate (PAH) were measured in blood and urine during five or six consecutive periods of 10 to 20 minutes duration. After a priming dose had been administered, the blood levels of mannitol and PAH were maintained approximately constant by intravenous administration of a 0.9% sodium chloride solution containing these substances, at a rate of 4 cc. per minute. Urine was collected by catheterization, and the bladder was rinsed with 0.9% sodium chloride solution at the end of each period. The analytical procedures used were essentially those employed by Goldring and Chasis (10).[4, 5] Among factors considered in performing the plasma and urine mannitol blanks were non-fermentable reducing substances contributed by plasma or urine, or "Factor 1," reducing substances contributed by the yeast suspension, or "Factor 2," and adsorption or destruction of mannitol by the yeast suspension, or "Factor 3." In performing the plasma blank, all three factors were corrected for, save in the case of the three subjects, L. C., I. H., and M. L., when compensation was made only for Factor 1. In performing the urine blank, Factors 2 and 3 were corrected for, save in the case of the same three subjects, when compensation was made only for Factor 2. Data on the technique employed for these blank determinations will be presented elsewhere (11).

The renal plasma clearances of mannitol and PAH were calculated using the formula "UV/P," where "U" and "P" are respectively concentration of the substance in urine and plasma, and "V" the volume of urine excreted per minute expressed in cubic centimeters (12). The value of P at the exact midpoint of each period was calculated by interpolation between the values observed during each period. The "filtration fraction" was calculated as the ratio of the mannitol clearance to the PAH clearance.

The afferent and efferent arteriolar resistances (R_A and R_E) were computed from our data according to Lam-

[1] This investigation was supported by a grant-in-aid from the National Institute of Health, United States Public Health Service.

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[4] The mannitol and PAH solutions administered were generously contributed by Sharpe and Dohme Company; the starch-free baker's yeast used in the mannitol analyses was given by Anheuser-Busch, Inc.

[5] Miss Ellabeth Houghton, Mrs. Mattie Heady and Mrs. Harriet Weil rendered technical assistance in performing and reporting the investigations.

TABLE I

Renal clearances of mannitol and para-aminohippurate (PAH) in five hypertensive subjects before and after histamine injection

Subject	Period	Histamine dose	Urine flow	Plasma levels: Mannitol	Plasma levels: PAH	Urine levels: Mannitol	Urine levels: PAH	Plasma clearances: Mannitol	Plasma clearances: PAH	Filt. frac.*	Blood pressure†	R_A‡	R_E§
		mgm.	*cc. per min.*	*mgm. per cc.*	*mgm. per cc.*	*mgm. per cc.*	*mgm. per cc.*	*cc. per min.*	*cc. per min.*		*mm. Hg*		
I. H. ♀	1		4.58	1.23	.0346	28.2	4.02	103	531	.193	160/100	0.0659	0.0117
193 lbs.	2		5.28	1.26	.0405	23.8	3.90	100	508	.198		.0685	.0127
64 in.	3	0.3	4.50	1.18	.0431	26.0	4.14	99	431	.230	135/90	.0543	.0183
40 years	4	0.2	5.12	1.17	.0468	28.2	4.75	123	530	.232	130/85	.0387	.0149
	5		5.12	1.18	.0473	27.4	4.61	119	500	.238	140/95	.0515	.0167
	6		4.28	1.12	.0450	29.5	4.89	112	464	.242	140/100	.0578	.0180
M. L. ♀	1		2.25	1.08	.0179	38.7	4.48	80.7	563	.143	170/105	0.0743	0.0076
199 lbs.	2		2.00	1.09	.0229	39.3	5.82	72.1	508	.142		.0825	.0084
60½ in.	3	0.4	1.94	1.08	.0266	46.2	6.92	89.8	504	.178	140/90	.0542	.0109
45 years	4		1.81	1.11	.0301	47.6	7.79	78.0	468	.167	170/95	.0810	.0112
	5		2.45	1.10	.0287	40.5	6.89	90.1	588	.163	170/105	.0693	.0090
D. B. ♀	1		3.18	1.42	.0269	41.1	3.72	91.8	439	.209	175/120	0.1050	0.0159
116 lbs.	2		3.21	1.36	.0285	42.1	4.04	99.6	455	.219	175/120	.0965	.0163
64¼ in.	3	0.4	2.06	1.30	.0350	52.6	5.58	83.2	328	.254	150/110	.0955	.0283
28 years	4		2.00	1.32	.0411	52.2	6.42	79.2	312	.254	150/110	.1010	.0298
	5		2.37	1.30	.0413	45.1	5.88	82.4	337	.244	165/115	.1120	.0256
F. W. ♀	1		1.70	1.54	.0347	41.3	4.67	45.7	229	.199	150/100	0.1392	0.0283
140 lbs.	2		1.61	1.50	.0358	41.1	5.46	44.4	245	.181	150/100	.1350	.0224
66¼ in.	3	0.15	1.72	1.46	.0415	39.9	5.17	47.0	214	.219	150/100	.1440	.0347
28 years	4		2.51	1.45	.0471	26.5	3.70	45.7	197	.232	130/100	.1242	.0400
	5		1.65	1.45	.0514	42.2	6.48	48.0	207	.232	150/110	.1600	.0382
L. C. ♀	1		3.71	.80	.0216	25.0	2.98	116.8	512	.228	210/130	0.1090	0.0154
234 lbs.	2		3.76	.79	.0249	25.7	3.32	122.0	501	.242	210/130	.1100	.0166
63½ in.	3		3.53	.79	.0281	26.2	4.06	118.0	511	.231	210/130	.1090	.0154
32 years	4	0.4	3.51	.88	.0349	28.5	5.04	114.0	508	.226	190/120	.0937	.0151
	5	0.3	2.29	.93	.0381	39.9	7.19	97.6	432	.226	165/105	.0838	.0177
	6		2.70	.95	.0389	37.7	6.48	106.3	449	.236	165/110	.0845	.0171

* Filt. frac. = filtration fraction = $\frac{\text{mannitol clearance}}{\text{PAH clearance}}$.

† Blood pressure = arterial blood pressure.

‡ R_A = afferent arteriolar resistance in mm. of mercury per cc. renal plasma flow per minute.

§ R_E = efferent arteriolar resistance in mm. of mercury per cc. renal plasma flow per minute.

port's formulae (13). In these computations we arbitrarily assumed a hematocrit of 0.43, a plasma protein concentration of 7.0 grams per 100 cc., and a ratio of albumin to globulin of 2.2. The injection of histamine did not influence the hematocrit values in the two experiments in which the measurement was made.

In addition to the 10 clearance experiments, the renal extraction of PAH and mannitol before and after subcutaneous administration of 0.5 mgm. of histamine was determined in three subjects by catheterization of the right renal vein,[6] using the technique devised by Cournand and Ranges (14) for the heart and developed by Warren, Brannon and Merrill (15) for the renal vein.[7] The blood pressure was measured in the arm by the auscultatory technique.

The dose of histamine was chosen so as to elicit a moderate general reaction with flushing of the face and headache. Lachrymation, palpitation, and tachycardia occurred in some patients; the blood pressure fell regularly only in hypertensive subjects. Usually 0.3 to 0.5 mgm. of histamine, calculated as the pure base, was administered, depending on body weight; in one case (F. W.) a marked reaction was produced by 0.15 mgm., and in another (L. C.) the administration of a total of 0.7 mgm. in two doses resulted in almost no reaction and no striking changes in renal clearances. The histamine

[6] The assistance of Dr. H. A. Schroeder in performing the catheterizations is gratefully acknowledged.

[7] Experiments in which clearance measurements and renal venous catheterizations were performed simultaneously showed a definite discrepancy between the mannitol clearance as usually calculated (UV/P) and the clearance computed from the calculated renal blood flow and the observed renal extraction of mannitol (23). However, we assume that for our purposes the clearance methods permit a useful approximation of kidney function.

TABLE II

Renal clearances of mannitol and para-aminohippurate (PAH) in five normotensive subjects before and after histamine injection *

Subject	Period	Histamine dose	Urine flow	Plasma levels		Urine levels		Plasma clearances		Filt. frac.	Blood pressure	R_A	R_E
				Mannitol	PAH	Mannitol	PAH	Mannitol	PAH				
		mgm.	*cc. per min.*	*mgm. per cc.*	*mgm. per cc.*	*mgm. per cc.*	*mgm. per cc.*	*cc. per min.*	*cc. per min.*		*mm. Hg*		
M. S. ♀	1		2.48	1.32	.0249	59.8	7.77	113	774	.146	110/60	0.0151	0.0055
113 lbs.	2		2.60	1.26	.0248	58.4	7.40	120	774	.154		.0147	.0058
68 in.	3	0.4	2.25	1.29	.0271	56.2	7.56	98	627	.156	110/60	.0182	.0072
25 years	4		2.65	1.28	.0279	55.3	8.09	115	767	.150	110/60	.0148	.0059
Asthenia	5		2.77	1.25	.0273	53.2	8.30	118	840	.141		.0142	.0048
M. C. ♀	1		2.91	1.30	.0209	45.6	5.99	102	835	.122	105/60	0.0136	0.0041
113 lbs.	2		2.22	1.24	.0212	50.0	6.62	89	693	.129		.0164	.0050
64 in.	3	0.5	2.88	1.24	.0221	49.9	6.87	115	896	.128	118/55	.0153	.0039
31 years	4		2.10	1.21	.0222	56.5	7.62	98	721	.135	115/50	.0154	.0052
Arthritis	5		2.21	1.13	.0230	58.0	7.58	113	729	.155	110/55	.0141	.0062
J. R. ♀	1		2.51	1.32	.0296	53.7	8.20	102	696	.147	130/80	0.0332	0.0061
180 lbs.	2		2.47	1.34	.0351	55.4	8.72	102	614	.166		.0361	.0081
62 in.	3	0.35	2.68	1.34	.0374	50.2	8.35	100	598	.167	125/85	.0371	.0084
22 years	4		2.06	1.34	.0381	54.5	8.96	84	485	.173		.0452	.0108
Neuro-syphilis	5		2.15	1.29	.0372	59.1	9.65	98	558	.176	125/85	.0394	.0094
F. C. ♂	1		2.15	0.99	.0243	50.7	9.44	109	834	.130	132/88	0.0322	0.0042
149 lbs.	2		2.09	1.00	.0239	39.5	8.28	82	723	.113	122/82	.0299	.0041
75 in.	3	0.4	1.54	0.92	.0254	45.9	7.37	76	446	.172	136/92	.0556	.0118
31 years	4		1.75	0.90	.0226	57.4	10.02	112	778	.144	132/92	.0334	.0055
Peptic ulcer	5		2.00	0.89	.0248	47.5	8.80	107	710	.151		.0360	.0063
C. F. ♀	1		1.48†	1.29	.0428	50.2	9.56	57†	330†	.174	90/55	0.0112	0.0158
94 lbs.	2		2.29†	1.21	.0388	54.1	9.64	102†	569†	.179	90/55	.0060	.0097
63½ in.	3	0.3	1.57	1.23	.0404	56.8	9.56	73	372	.195	100/55	.0146	.0167
21 years	4		1.73	1.22	.0426	52.7	8.45	74	343	.217		.0079	.0132
Peptic ulcer	5		1.60	1.19	.0386	57.8	9.30	78	385	.202	100/55	.0133	.0168

* See Table I footnotes for abbreviations.
† Residual urine in the bladder after the first period may account for these differences.

was administered subcutaneously as the acid phosphate in a solution containing 1 mgm. of the pure base in 1 cc. Renal clearance measurements were made for two or three control periods before injecting histamine.

RESULTS

The most constant changes in renal clearances after the injection of histamine were a decrease, as indicated by the PAH clearance (16), in the plasma flow and an associated increase in the filtration fraction. The filtration rate, as measured by the mannitol clearance (17), was not consistently altered (Tables I, II). These characteristic features are summarized in Table III. In Figure 1 are presented schematically the mean values observed in both the hypertensive and non-hypertensive groups. In the normotensive subjects, there appeared to be no correlation between the reduction in renal plasma flow and the systemic blood pressure, the latter showing a very variable behavior. The frequent elevation in the filtration fraction in both groups of subjects indicates that active arteriolar constriction occurred. It has been generally assumed that spasm of the efferent arterioles accounts for this elevation of the filtered portion of plasma passing through the kidney (18).

Whereas four out of five hypertensive individuals showed a definite rise in the filtration fraction, such an elevation was evident in only two normotensive subjects; in two others it was questionable, occurring slowly possibly because of spontaneous changes in arteriolar tone unrelated to the injection of histamine (18). In one hypertensive subject and one normotensive subject there were no changes in filtration fraction. The average curves (Figure 1) indicate that the mean increase in filtration fraction was about the same in both series, amounting to 12% in the normotensive group and 14% in the hypertensive patients. Two normotensive individuals appeared to be very sensitive to the injected amine.

The calculated efferent arteriolar resistance was increased in four and unchanged in one hypertensive subject. It was also increased in four (in three only slightly) and unchanged in one normotensive individual. The afferent arteriolar resistance was decreased in three and unchanged in two hypertensive patients; in normotensive subjects, changes were roughly parallel to those in the efferent resistance.

As will be seen in Table IV, the renal extraction percentage of mannitol and PAH was not consistently influenced by the injection of histamine. The data on subject F. C. presented in Tables II and IV were obtained during the same experiment.

Qualitative (heat) tests on the urine of nine of the ten patients revealed no proteinuria occurring during the clearance period immediately following the injection of histamine. The tenth patient (I. H.) exhibited traces of urinary protein antecedent to the injection of histamine; the injection caused no immediate increase in proteinuria.

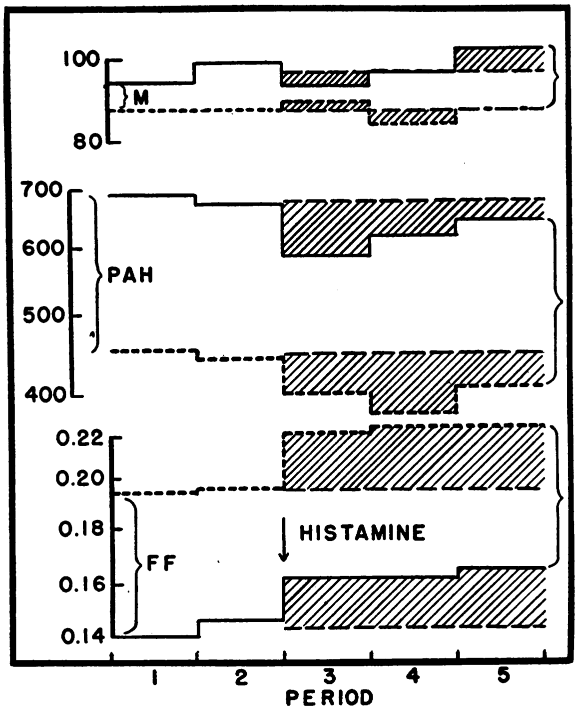

Fig. 1. Schematic Presentation of Averages for Renal Clearances and Filtration Fraction (FF)

Broken line presents data on five hypertensive subjects (Table I); solid line on five normotensive subjects (Table II). Histamine injected at start of third period. Clearances of para-aminohippurate (PAH) and mannitol (M) expressed as cc. plasma per minute.

TABLE III

Qualitative variations in renal function and in blood pressure in normotensive and hypertensive subjects following the injection of histamine

Subject	Plasma flow	Filtration rate	Filtration fraction	Blood pressure	R_A	R_E
Hypertensive						
I. H.	d.	i.	i.	d.	d.	i.
M. L.	s.d.	i.	i.	d.	d.	i.
D. B.	d.	d.	i.	d.	u.	i.
F. W.	s.d.	s.i.	i.	d.	u.	i.
L. C.	d.	d.	u.	d.	d.	u.
Normotensive						
M. S.	d.	d.	u.	u.	s.i.	s.i.
M. C.	u.	u.	u.*	i.	u.	u.*
J. R.	d.	d.	u.*	u.	s.i.	s.i.
F. C.	d.	s.d.	i.	s.i.	i.	i.
C. F.	d.	s.d.	i.	s.i.	s.i.	s.i.

* Actually slightly increased but probably not significantly.

i. = increased. d. = decreased. s.i. = slightly increased. s.d. = slightly decreased. u. = unchanged.

DISCUSSION

From these observations it would appear that the reduction in renal plasma flow following the subcutaneous administration of histamine was often due to efferent arteriolar constriction. In some cases (M. S., J. R.), in whom there was observed no change in filtration fraction, it seems likely that constriction of the afferent arteriole took place. The fall in systemic blood pressure may have played a part in reducing renal plasma flow in patient L. C.

It is known that histamine may produce vasoconstriction of arterioles, but constriction alone, wherever it might take place in the kidney, would hardly account for the absolute increase in the mannitol clearance simultaneous with a fall in systemic blood pressure observed in two hypertensive patients (I. H. and M. L.). With efferent arteriolar constriction, if relaxation of afferent arteriolar tone or increased permeability of glomeru-

TABLE IV

Renal extraction of mannitol and para-aminohippurate (PAH) in three subjects before and after injection of histamine

Subject	Time after histamine 0.5 mgm.	Para-aminohippurate				Mannitol			
		Peripheral vein level	Renal vein level	Difference	Extraction	Peripheral vein level	Renal vein level	Difference	Extraction
	minutes	*mgm. per cc.*	*mgm. per cc.*	*mgm. per cc.*	%	*mgm. per cc.*	*mgm. per cc.*	*mgm. per cc.*	%
B. C. ♂	Before	.0314	.0095	.0219	69.8	1.19	1.05	0.14	11.7
26 yrs.	6	.0327	.0084	.0243	74.3	1.22	1.06	0.16	13.1
Hypertension	20	.0311	.0092	.0219	70.5	1.19	1.04	0.15	12.6
	24	.0306	.0084	.0222	72.5	1.18	1.04	0.14	11.9
	42	.0288	.0078	.0210	73.0	1.15	0.95	0.20	17.4
F. C. ♂	Before	.0241	.0014	.0227	94.0	1.000	0.811	0.189	18.9
31 yrs.	Before	.0239	.0015	.0224	93.8	1.003	0.841	0.162	16.2
Peptic	3	.0242	.0018	.0224	92.7	0.979	0.757	0.222	22.7
ulcer	9	.0255	.0019	.0236	92.7	0.924	0.750	0.174	18.8
	17	.0249	.0022	.0227	91.3	0.909	0.778	0.131	14.4
	31	.0227	.0017	.0210	92.6	0.897	0.778	0.119	13.3
	45	.0247	.0017	.0230	93.0	0.890	0.745	0.145	16.3
A. B. ♂	Before	.0492	.0095	.0397	80.7	1.37	1.16	0.21	15.3
44 yrs.	Before	.0493	.0093	.0400	81.0	1.35	1.17	0.18	13.4
Hypertension	Before	.0480	.0090	.0390	81.2	1.36	1.13	0.23	16.9
	5	.0514	.0093	.0421	81.8	1.37	1.11	0.26	19.0
	21	.0534	.0105	.0429	80.2	1.42	1.15	0.27	19.0
	37	.0498	.0114	.0384	77.0	1.39	1.16	0.23	16.5

lar endothelium did not occur, one would expect little change in or a reduction of the filtration rate. The occurrence of afferent arteriolar relaxation seems to be supported by the experiment on patient I. H. presented in Table I. In the third period there was no change in the mannitol clearance, but blood flow was significantly reduced. This finding can be related to efferent arteriolar constriction. After the second injection of histamine at the start of the fourth period, however, there was a sudden increase in both PAH and mannitol clearances, the former reaching its previous level, the latter rising markedly above it. As the filtration fraction remained practically unchanged concurrent with these increases, relaxation of afferent arterioles can be considered as probably responsible for this phenomenon. Further evidence in favor of this view is found in the values for efferent and afferent arteriolar resistance; the former increased during the third period, the latter decreased during the fourth. Change in permeability of glomerular endothelium could not of itself account for the observed increase in the PAH clearance. As regards possible increased glomerular permeability, it is of interest that the slight proteinuria observed in this patient before histamine was administered did not increase.

A significant increase in the filtration rate without simultaneous reduction of renal blood flow was also evident in subject M. L. (Figure 2). Here again two interpretations are possible—efferent arteriolar spasm plus afferent relaxation, or increased endothelial permeability. The first possibility seems to be enhanced by the behavior of efferent and afferent resistance, since the former increased from 0.0084 mm. of mercury per cc. of plasma per minute to 0.0109 and the latter decreased from 0.0825 to 0.0542. It is worthy of emphasis that this absolute increase in the filtration rate did not occur in any of our normotensive subjects, suggesting that the glomerulus of the hypertensive kidney may react in a characteristic manner.

We therefore interpret our data bearing on the state of the afferent glomerular artery as indicating that in some subjects the administration of histamine produces constriction, and in others either no effect on, or relaxation of, this vessel. Relaxation was observed only within the hypertensive group of subjects.

There was no consistently pronounced effect of the injection of histamine upon the urine volume. Changes in the reabsorption of water seemed to occur spontaneously, more or less independently of the filtration rate. Data obtained from analysis

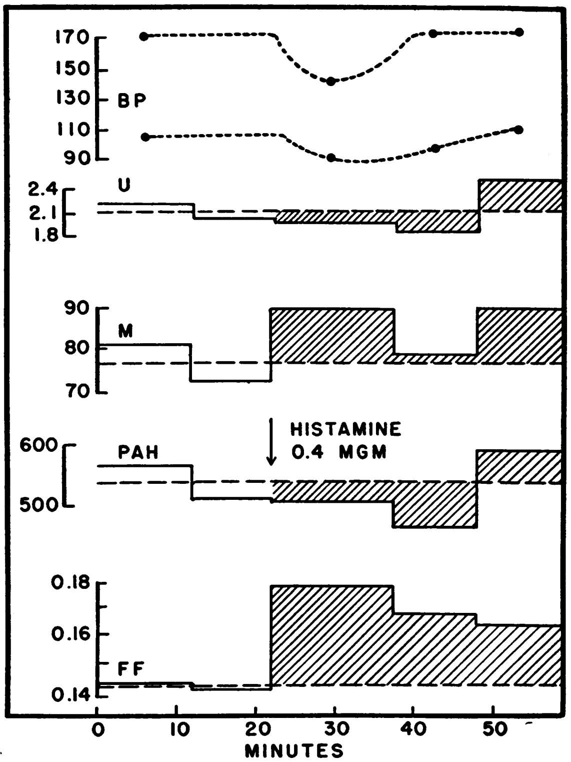

FIG. 2. EFFECT OF HISTAMINE UPON RENAL FUNCTION OF HYPERTENSIVE SUBJECT M. L.

Abbreviations and units as in Figure 1. Blood pressure (BP) expressed as mm. mercury, and urine flow (U) as cc. per minute.

of renal venous blood (Table IV) indicate that the extraction of PAH was not reduced after histamine, so that impairment of tubular function, which might explain a fall in PAH clearance, seems unlikely.

Our findings indicate that the kidney of hypertensive subjects does not appear to be on the whole much more sensitive to the action of histamine than that of normotensive subjects, at least in this small series. Moreover, individual susceptibility seems to vary widely. Noteworthy perhaps is the different behavior of the afferent arteriolar resistance in both groups. The average efferent resistance was increased from 0.0068 to 0.0088 in the normotensive and from 0.0155 to 0.0216 in the hypertensive subjects. The average afferent resistance rose after histamine from 0.0208 to 0.0249 in the normotensive but fell from 0.0995 to 0.0878 in the hypertensive group. This fall is possibly related to the fact that R_A is already very high in the latter group (19).

It is uncertain whether the observed effects upon renal physiology were due to histamine alone, or whether the action of epinephrine was involved. It is conceivable that in our experiments the administration of histamine, itself possibly inactive upon the kidney, induced a response due to adrenalin; such an effect of histamine may occur in patients with pheochromocytoma (20, 21). There is little doubt that the effects of histamine upon renal arteriolar tone are similar in some respects to those of epinephrine.

The reaction of the efferent arteriole to histamine must be emphasized, as it is elicited in this case by a so-called "hypotensive" amine. It appears that various drugs are capable of inducing an elevation in filtration fraction similar to that found persistently in hypertensive subjects.[8]

The possibility that histamine may play a part in the pathogenesis of glomerular nephritis has already been referred to. If the action of histamine is involved in the etiology of the disease, on the basis of our observations it might be expected that the filtration fraction would be found to be higher than normal. Earle *et al.* (22), however, observed an abnormally low filtration fraction in glomerular nephritis. The two patients studied by those authors who were in initial stages of their disease had manifested symptoms for three and five weeks. At this stage alterations of the capillaries may have reduced the "filtering bed." Studies performed during the very first days of the disease would provide a more acceptable basis for evaluating the possible role of histamine in its pathogenesis.

SUMMARY

1. The effect of a subcutaneous injection of histamine upon renal function was investigated in five hypertensive and five normotensive subjects

[8] In an additional patient with hypertension studied after this work had been completed, a large dose of histamine (0.5 mgm.) produced a dramatic reaction with pallor and palpitation. The filtration fraction *decreased* from 0.256 to 0.100 consequent to a fall in mannitol and an elevation in PAH clearance. These findings suggested efferent arteriolar relaxation, or, as the urine flow was markedly reduced, a back diffusion of mannitol through the tubular walls. Blood pressure was not measured. Although this picture was observed only in one instance, it indicates how the effects of the same drug may vary with the susceptibility of the patient.

with the aid of measurements of the mannitol and para-aminohippurate clearances.

2. Four of five hypertensive subjects responded with an increase in the filtration fraction and efferent arteriolar resistance, probably caused by a constriction of efferent glomerular arterioles. In two of the four patients, this constriction was accompanied either by relaxation of the afferent glomerular arteriole (decreased afferent resistance), or, less likely, by increased glomerular permeability. In the fifth subject there occurred a proportional reduction of renal blood flow and filtration rate in spite of decreased afferent resistance, probably related to a fall in blood pressure.

3. In four of five normotensive patients, there were observed manifestations of efferent and afferent arteriolar constriction. One normotensive subject showed no change in renal clearance following administration of histamine.

4. Significant changes in the urine volume were not regularly observed.

5. The renal extraction of para-aminohippurate did not change after administration of histamine in three subjects.

BIBLIOGRAPHY

1. Dale, H. H., and Laidlaw, P. P., The physiological action of β-imidazolylethylamine. J. Physiol., 1910–1911, **41**, 318.
2. Morimoto, M., Über die Wirkung von Histamin auf die Nierengefässe. Arch. f. exper. Path. u. Pharmakol., 1928, **135**, 194.
3. Rothlin, E., Experimentelle Studien über die Eigenshaften überlebender Gefässe unter Anwendung der chemischen Reizmethode. Biochem. Ztschr., 1920, **111**, 219.
4. Dicker, E., A propos de l'hypertension artérielle consécutive à une entrave de la circulation rénale. Compt. rend. Soc. de biol., 1937, **125**, 1946.
5. Bjering, T., The influence of histamine on renal function. Acta med. Scandinav., 1937, **91**, 267.
6. Reubi, F. C., L'influence des antihistaminiques de synthèse sur le développement et l'évolution de la néphrite expérimentale. Helvet. med. acta., 1945, **12**, 547.
7. Reubi, F. C., Le traitement de la néphrite aiguë par les antihistaminiques de synthèse. Helvet. med. acta., 1946, **13**, Supp. 18.
8. Schroeder, H. A., and Steele, J. M., Studies on "essential" hypertension; classification. Arch. Int. Med., 1939, **64**, 927.
9. Schroeder, H. A., Personal communication.
10. Goldring, W., and Chasis, H., Hypertension and Hypertensive Disease. The Commonwealth Fund, New York, 1944.
11. Futcher, P. H., and Houghton, E., In preparation.
12. Möller, E., McIntosh, J. F., and Van Slyke, D. D., Studies of urea excretion. II. Relationship between urine volume and the rate of urea excretion by normal adults. J. Clin. Invest., 1928, **6**, 427.
13. Lamport, H., Improvements in calculation of renal resistance to blood flow. Charts for osmotic pressure and viscosity of blood. J. Clin. Invest., 1943, **22**, 461.
14. Cournand, A., and Ranges, H. A., Catheterization of the right auricle in man. Proc. Soc. Exper. Biol. and Med., 1941, **46**, 462.
15. Warren, J. V., Brannon, E. S., and Merrill, A. J., A method of obtaining renal venous blood in unanesthetized persons with observations on the extraction of oxygen and sodium para-amino hippurate. Science, 1944, **100**, 108.
16. 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.
17. Smith, W. W., Finkelstein, N., and Smith, H. W., Renal excretion of hexitols (sorbitol, mannitol and dulcitol) and their derivatives (sorbitan, isomannide and sorbide) and of endogenous creatinine-like chromogen in dog and man. J. Biol. Chem., 1940, **135**, 231.
18. Smith, H. W., Physiology of the renal circulation. The Harvey Lectures, 1939–40, Series 35, 166, Science Press, Lancaster, Pa.
19. Corcoran, A. C., Taylor, R. D., and Page, I. H., Functional patterns in renal disease. Ann. Int. Med., 1948, **28**, 560.
20. Roth, G. M., and Kvale, W. F., A tentative test for the diagnosis of pheochromocytoma. J. Lab. & Clin. Med., 1945, **30**, 366.
21. Horton, B. T., Discussion of material presented in reference 20 above. J. Lab. & Clin. Med., 1945, **30**, 367.
22. Earle, D. P., Jr., Taggart, J. V., and Shannon, J. A., Glomerulonephritis. A survey of the functional organization of the kidney in various stages of diffuse glomerulonephritis. J. Clin. Invest., 1944, **23**, 119.
23. Reubi, F. C., The renal extraction of mannitol and para-aminohippurate compared to their excretions in normotensive and hypertensive subjects. J. Clin. Invest., 1948, **27**, 553.