RENAL CIRCULATORY DYNAMICS AND URINARY PROTEIN EXCRETION DURING INFUSIONS OF *l*-NOREPINEPHRINE AND *l*-EPINEPHRINE IN PATIENTS WITH RENAL DISEASE [1, 2]

By WILLOUGHBY LATHEM [3]

(From The Department of Internal Medicine, Yale University School of Medicine, and the Veterans Administration Hospital, West Haven, Conn.)

(Submitted for publication June 25, 1956; accepted August 2, 1956)

That hemodynamic adjustments within the kidney may modify the rate of transport of protein molecules across glomerular capillary membranes has been suggested by a variety of experimental studies. The mechanisms which alter protein transport under these conditions are not clear, but since proteins apparently traverse capillary walls by diffusion as well as filtration (2), differing mechanisms may play a role depending on the nature and circumstances of the associated vascular adjustments. Thus filtration may be modified under conditions which alter intraglomerular hydrostatic pressure (3–5) and diffusion under circumstances which influence the rate of formation of glomerular filtrate (2). It has been suggested that protein transport and urinary protein excretion may be altered by renal circulatory adjustments which modify the area available for transport within the kidney (6) or which influence the integrity of the capillary wall (7–9). Moreover, it has recently been suggested that protein transport may also be conditioned by the velocity of blood flow through the glomerulus (10).

In the present study an examination of these factors was undertaken in patients with renal disease and proteinuria. The urinary excretion and renal clearance of plasma proteins were determined under circumstances in which intrarenal circulatory adjustments were induced by the administration of the adrenal medullary hormones, *l*-norepinephrine and *l*-epinephrine.

[1] This study was supported by a grant-in-aid from the National Heart Institute, U. S. Public Health Service, and from the American Heart Association and Greenwich Health Association.

[2] The results of this study have appeared in part in abstract form (1).

[3] Present address: Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

METHOD

The effects of *l*-norepinephrine on the renal clearances of inulin, sodium p-aminohippurate (PAH) and plasma proteins were determined in 16 patients, and the effects of *l*-epinephrine were determined in 7 patients, with well-documented chronic renal disease (Table I). The subjects, who varied in age from 19 to 64 years, were all males with the exception of E. Z. All had a consistently demonstrable proteinuria, ranging from a trace to 4 plus, as determined by the sulfosalicylic acid test. All studies were made in fasting subjects after the ingestion of 500 ml. of water approximately one hour prior to the test. After the subjects had been lying quietly in bed for at least one hour three control clearance periods of 10 to 15 minutes each were obtained. The arterial blood pressure, measured sphygmomanometrically, and radial pulse rate were recorded at frequent intervals during the control observations. Upon completion of the control measurements an intravenous infusion of *l*-norepinephrine or *l*-epinephrine was started. *L*-norepinephrine, made up in 5 per cent dextrose (8 μg. per ml.), was administered at a rate sufficient to elevate the systolic blood pressure 20 to 50 mm. Hg. The amount required for this purpose varied from 3 to 72 μg. per minute and usually required 15 to 20 μg. per minute. After the blood pressure, which was measured at one to two-minute intervals, had stabilized at the desired level for approximately 15 minutes, the urine was discarded and three 10 to 15-minute clearance periods were obtained during the pressor response to *l*-norepinephrine. In 8 subjects three 10 to 15-minute clearance periods were collected immediately after the infusion of *l*-norepinephrine had been discontinued.

The design of the experiments in which the effects of *l*-epinephrine [4] were studied was similar to that employed in the study of *l*-norepinephrine except that *l*-epinephrine was administered at a rate insufficient to elevate the arterial blood pressure significantly. This agent was made up in 5 per cent dextrose in a concentration of 2 μg. per ml. and was infused at a rate of from 2 to 6 μg. per minute. Recovery periods were obtained in 4 of these subjects after cessation of the infusion.

Glomerular filtration rate was measured as the inulin clearance (11) and renal plasma flow as the PAH

[4] Supplied by Parke, Davis & Co., Detroit, Mich.

TABLE I

Renal hemodynamics and urinary protein excretion during infusion of adrenal medullary hormones *

Subject Diagnosis Age	S.A. M^2	BUN mgm. %	Procedure	B.P. mm. Hg	P.R. per min.	T.P. gm. %	Hct. %	C_{in} ml./min.	C_{pah} ml./min.	FF %	$U_{pr}V$ mgm./min.	C_{pr} ml./min.	C_{pr}/C_{in} $\times 10^{-3}$
						l-Norepinephrine							
R. H. Chronic glom. neph. 27	1.78	15	Control	124/76	68	5.00	42.5	136	735	18.8	1.1	0.023	0.17
			Infusion	176/104	56	5.25	42.3	127	469	27.1	16.6	0.316	2.49
			Recovery	130/78	76	5.10	42.6	147	615	23.9	5.1	0.100	0.68
T. P. Amyloid 19		15	Control	120/80	96	4.90	47.0	133	672	19.8	1.6	0.033	0.25
			Infusion	144/100	72	5.10	47.7	127	519	24.5	3.3	0.065	0.51
J. D. Tbc. 52	1.74	17	Control	122/72	68	5.70	44.1	125	595	21.0	0.3	0.006	0.05
			Infusion	160/80	62	5.60	45.6	131	495	26.5	0.5	0.010	0.08
			Recovery	124/70	68	5.60	45.0	118	550	21.5	0.3	0.006	0.05
A. B. Chronic glom. neph. 23	1.88	14	Control	128/70	60	6.00	45.7	106	505	21.0	0.6	0.009	0.09
			Infusion	170/90	48	6.10	48.3	83	236	35.2	1.6	0.025	0.30
			Recovery	130/60	72	6.00	47.2	127	567	22.4	1.5	0.024	0.19
A. McG. Chronic glom. neph. 23	1.72	18	Control	94/60	64	6.42	45.2	103	503	20.5	0.4	0.006	0.06
			Infusion	130/88	56	7.05	48.4	90	306	29.4	0 8	0 011	0.12
			Recovery	100/60	80	6.50	45.1	90	478	18.8	0.7	0.010	0.11
A. K. (A) Amyloid 59	1.70	19	Control	106/80	84	5.60	52.9	94	218	44.0	0.9	0.017	0.18
			Infusion	150/86	74	6.45	57.2	89	133	66.0	4.0	0.063	0.71
J. O'B. Amyloid 46	1.58	19	Control	90/60	120	4.17	46.7	86	310	27.8	9.9	0.238	2.77
			Infusion	130/80	100	4.30	48.9	91	239	38.0	16.1	0.376	4.13
T. D. Chronic glom. neph. 31	1.94	16	Control	120/92	70	5.00	46.6	86	445	19.3	2.1	0.043	0.50
			Infusion	154/100	60	5.55	47.8	76	296	25.7	11.8	0.212	2.78
P. L. (A) Chronic pyelo. 60	2.06	18	Control	120/90	86	5.40	43.3	69	212	32.6	1.6	0.030	0.44
			Infusion	140/100	80	5.65	44.2	68	178	38.2	2.8	0.049	0.72
			Recovery	128/90	84	5.45	42.9	70	214	32.7	2.5	0.046	0.66
E. Z. Kimmel-Wilson 56	1.60	25	Control	122/60	82	4.70	37.7	68	496	13.7	4.8	0.103	1.52
			Infusion	170/80	88	4.60	37.6	66	363	18.2	10.5	0.206	3.12
J. C. Chronic pyelo. 25	1.60	19	Control	110/78	84	8.52	36.8	64	227	28.2	0.3	0.003	0.05
			Infusion	162/102	52	9.05	40.4	65	193	33.6	0.5	0.005	0.08
J. B. Chronic glom. neph. 37	1.82	22	Control	140/100	68	7.40	40.0	49	184	26.4	0.3	0.004	0.08
			Infusion	174/120	60	7.45	41.5	44	200	22.0	0.3	0.003	0.07

* All values are averages of three determinations. *L*-norepinephrine or *l*-epinephrine was administered intravenously during the infusion periods. The recovery periods were obtained immediately after the infusion was discontinued. Abbreviations are as follows:

S.A. = body surface area (M^2).
BUN = blood urea nitrogen.
B.P. = arterial blood pressure.
P.R. = pulse rate.
T.P. = total serum protein concentration.
Hct. = hematocrit of venous blood.
C_{in} = inulin clearance.
C_{pah} = sodium p-aminohippurate clearance.
FF = renal filtration fraction (C_{in}/C_{pah}).
$U_{pr}V$ = urinary protein excretion.
C_{pr} = protein clearance.
C_{pr}/C_{in} = protein-inulin clearance ratio.

TABLE I—*Continued*

Subject Diagnosis Age	S.A. M^2	BUN mgm. %	Procedure	B.P. mm. Hg	P.R. per min.	T.P. gm. %	Hct. %	C_{in} ml./min.	C_{pah} ml./min.	FF %	$U_{pr}V$ mgm./min.	C_{pr} ml./min.	C_{pr}/C_{in} $\times 10^{-3}$
						l-Norepinephrine—*Continued*							
W. E. Amyloid 59	1.52	34	Control	90/60	64	4.20	35.6	35	95	36.9	1.3	0.032	0.92
			Infusion	120/74	66	4.25	39.8	29	68	41.6	2.5	0.059	2.04
			Recovery	90/60	70	4.00	35.0	41	120	34.2	2.9	0.072	1.75
E. B. Nephro-sclerosis 64	1.56	30	Control	172/84	80	6.30	43.9	34	159	21.4	0.4	0.006	0.18
			Infusion	198/90	72	6.40	44.1	38	172	22.1	0.5	0.007	0.18
J. H. Chronic pyelo. 63	1.63	52	Control	134/80	80	5.40	43.9	32	105	30.4	4.9	0.091	2.84
			Infusion	160/94	84	5.45	45.3	16	49	32.6	4.6	0.084	5.25
			Recovery	142/80	84	5.40	43.5	36	125	28.8	8.0	0.148	4.12
P. B. Polycystic 54	2.06	58	Control	166/94	72	6.10	34.8	16	62	25.8	0.9	0.014	0.88
			Infusion	190/94	64	6.05	35.9	13	57	22.8	0.7	0.012	0.93
			Recovery	160/92	68	5.60	33.6	15	71	21.2	0.9	0.016	1.07
						l-Epinephrine							
A. K. (B) Amyloid 59	1.70	15	Control	120/70	100	6.40	57.0	103	264	39.0	1.3	0.020	0.19
			Infusion	126/70	96	6.55	55.7	112	214	52.4	2.1	0.032	0.29
P. L. (B) Chronic pyelo. 60	2.06	19	Control	114/78	56	6.10	45.5	66	262	25.2	2.7	0.045	0.68
			Infusion	124/74	56	6.65	47.5	69	216	32.3	5.9	0.089	1.29
			Recovery	126/78	56	6.00	45.8	68	227	30.4	4.5	0.076	1.12
O. B. Nephro-sclerosis 63	1.86	20	Control	150/110	108	6.60	49.8	59	132	44.6	4.2	0.064	1.08
			Infusion	156/100	108	6.65	49.8	37	112	33.0	3.5	0.052	1.41
S. R. Chronic pyelo. 62	1.80	24	Control	130/80	84	5.85	43.2	57	193	29.9	1.6	0.027	0.47
			Infusion	130/70	92	5.75	44.2	44	153	28.8	1.6	0.028	0.64
L. K. Chronic glom. neph. 37	2.17	21	Control	148/110	60	5.85	48.7	51	239	21.3	1.0	0.017	0.33
			Infusion	140/100	72	5.90	49.2	47	172	27.3	1.2	0.021	0.45
			Recovery	136/100	68	5.95	48.9	49	196	25.0	1.3	0.022	0.45
J. M. Chronic pyelo. 58	1.80	34	Control	130/72	68	6.00	37.7	43	183	23.5	0.7	0.012	0.29
			Infusion	124/70	68	6.05	37.9	38	160	23.8	0.7	0.012	0.32
			Recovery	122/70	68	5.70	36.1	37	176	21.0	0.7	0.012	0.32
J. R. Nephro-sclerosis 60	1.76	47	Control	250/160	84	6.40	49.6	23	100	23.0	3.6	0.057	2.48
			Infusion	250/140	96	6.90	50.8	9	85	10.6	2.7	0.040	4.44
			Recovery	254/158	88	6.10	47.8	23	118	19.5	3.1	0.052	2.26

clearance (11). The concentration of protein in serum and urine was determined by the biuret method (12). In 16 subjects serum and urinary protein patterns were determined by paper electrophoresis. In order to increase the protein concentration of urine to levels sufficient to permit accurate evaluation by electrophoresis, aliquots of pooled urine collected during the control, infusion and recovery periods were dialyzed at a temperature of 4° C. in Visking cellophane bags against 12 per cent Dextran. Dialysis was continued until the concentration of protein in the urine approximated 60 mgm. per ml. Ten-μl. aliquots of pooled, concentrated urine and serum were applied to Whatman No. 3 filter paper and electrophoresis was carried out in a Durrum-type cell at 110 volts and 6 mA (for 8 strips) for a period of 16 hours. Diethylbarbituric acid-sodium barbital buffer of pH 8.6 and ionic strength 0.1 was employed. The paper strips were stained with bromphenol blue and the relative propor-

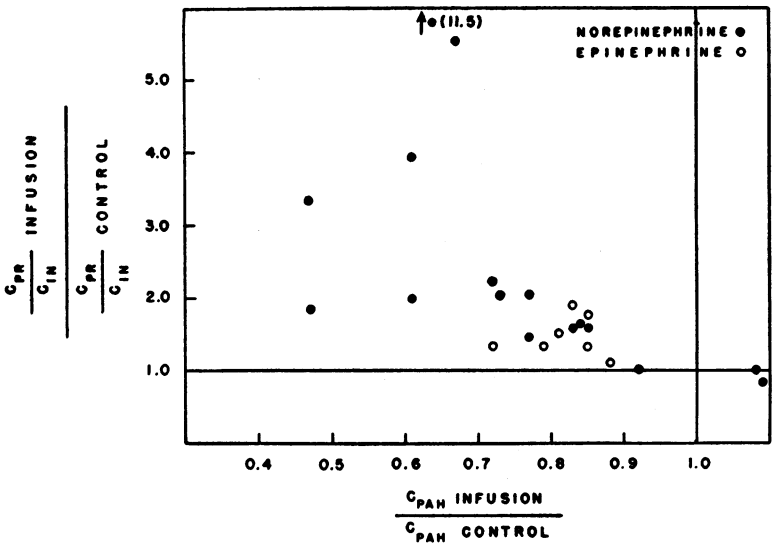

FIG. 1. RELATIONSHIP OF THE ALTERATIONS IN THE PROTEIN-INULIN CLEARANCE RATIO TO THE CHANGES IN PAH CLEARANCE DURING INFUSIONS OF *l*-NOREPINEPHRINE AND *l*-EPINEPHRINE

The protein-inulin clearance ratio during the infusion of adrenal medullary hormones relative to control values is plotted against the PAH clearance during infusion of these agents relative to control values. As the PAH clearance decreased below 85 per cent of control levels, protein clearance tended to rise relative to filtration.

tions of the individual protein fractions were determined by dye-elution. The filter paper was cut between each protein fraction at the point of lowest dye concentration as judged by the unaided eye and each fraction was eluted with 0.01 N NaOH for 30 minutes. After elution the optical density of the eluate was determined in a Coleman Universal spectrophotometer at a wavelength of 575 mμ. The amount of sodium hydroxide used was adjusted so that the optical densities of the respective fractions of the control, infusion and recovery periods were approximately equal. When determined in this manner the error of the method for measurement of the individual protein fractions was: for albumin, 1.9 per cent; α_1 globulin, 4.2 per cent; α_2 globulin 2.9 per cent; β globulin, 1.8 per cent; and γ globulin, 2.1 per cent.

The hematocrit of venous blood was determined in Wintrobe hematocrit tubes which were centrifuged for 30 minutes at 3,000 rpm. The blood urea nitrogen was determined by the method of Böger and Wezler (13).

RESULTS

The effects of *l*-norepinephrine and *l*-epinephrine on renal hemodynamics and urinary protein excretion are presented in Tables I and II and are illustrated in Figures 1 to 3.

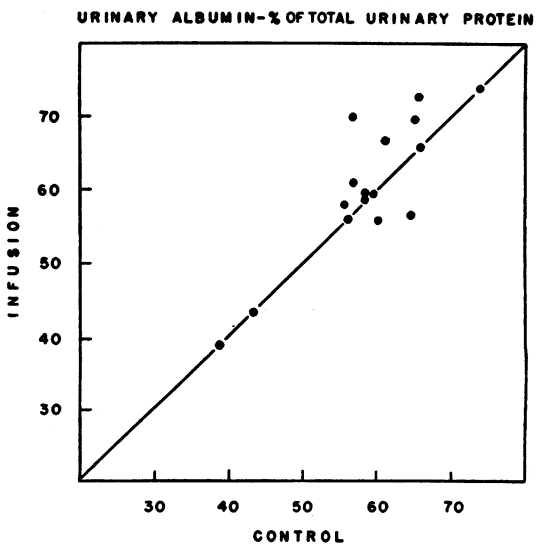

FIG. 2. URINARY ALBUMIN EXCRETION

Urinary albumin, expressed as percentage of the total urinary protein, during the infusion of *l*-norepinephrine and *l*-epinephrine is plotted against the control percentages. Only those subjects in whom the protein-inulin clearance ratio increased are included. The relative proportions of urinary albumin did not change during infusion of the adrenal medullary hormones.

TABLE II

Individual urinary and serum proteins during infusions of adrenal medullary hormones *

Subject	Procedure	Urine					Serum				
			Globulins					Globulins			
		Alb. %	α_1 %	α_2 %	β %	γ %	Alb. %	α_1 %	α_2 %	β %	γ %
					l-Norepinephrine						
R. H.	Control	65.6	7.4	6.0	9.6	11.4	50.0	5.6	16.1	13.6	14.6
	Infusion	72.6	5.6	6.5	9.1	6.2	49.8	5.8	16.0	13.7	14.6
	Recovery	74.8	6.0	4.8	8.4	6.0	51.0	5.1	16.0	13.9	14.9
T. P.	Control	61.0	10.1	8.7	9.9	10.3	29.9	5.7	17.9	21.1	25.5
	Infusion	66.8	9.5	7.0	8.7	7.9	33.8	5.9	17.9	17.5	25.0
A. K. (A)	Control	58.3	9.5	6.8	13.9	11.5					
	Infusion	59.6	8.8	7.5	13.8	10.3					
J. O'B.	Control	38.6	16.1	19.5	10.1	15.6	5.0	5.5	43.9	25.5	20.1
	Infusion	39.0	15.5	20.1	10.0	15.4	5.2	5.0	43.8	25.7	20.3
T. D.	Control	56.7	12.4	10.3	10.8	9.8	45.9	7.3	16.0	16.0	14.8
	Infusion	69.9	8.0	6.2	9.2	6.7	46.2	7.3	15.8	15.9	14.8
P. L. (A)	Control	65.8	10.6	6.3	10.2	7.0	37.2	7.3	12.8	16.8	25.9
	Infusion	65.8	10.9	6.8	9.9	6.5	37.8	7.3	12.4	16.6	25.9
	Recovery	62.8	9.8	6.9	10.0	10.5					
E. Z.	Control	56.0	14.3	9.5	12.2	8.0	29.9	8.2	35.5	12.1	14.3
	Infusion	56.0	13.3	9.6	13.2	7.9	28.3	8.0	37.0	12.0	14.6
W. E.	Control	65.0	8.4	8.4	12.0	5.8	40.1	10.0	21.0	16.7	12.3
	Infusion	69.6	7.6	7.6	10.5	4.7	43.1	10.7	18.5	16.1	11.7
	Recovery	64.0	8.6	9.7	11.8	5.9					
J. H.	Control	59.5	10.2	8.3	12.1	9.9	33.0	7.9	18.5	18.3	22.4
	Infusion	59.8	9.1	8.1	11.8	11.1	32.2	8.1	18.3	17.7	23.8
	Recovery	54.5	11.0	11.1	14.0	9.4	34.6	8.2	17.5	18.3	21.5
P. B.	Control	64.4	16.2†		8.9	10.5	52.4	6.5	12.3	15.6	13.2
	Infusion	56.8	17.8†		11.2	10.9	52.7	7.1	11.1	16.3	12.8
	Recovery	67.9	13.4†		10.3	8.5	52.5	6.0	12.0	15.1	13.4
					l-Epinephrine						
A. K. (B)	Control	56.8	8.7	6.2	14.5	13.8	39.3	6.1	12.1	17.7	24.7
	Infusion	61.0	7.3	6.8	14.2	10.7	38.0	6.6	11.0	17.9	26.4
P. L. (B)	Control	60.0	8.2	7.3	15.3	9.1	30.4	5.8	11.9	15.1	36.8
	Infusion	55.8	8.6	7.8	16.5	11.4	30.1	5.9	12.9	14.6	36.4
	Recovery	55.4	7.4	6.8	14.9	8.7	30.4	6.5	11.3	15.2	36.8
O. B.	Control	58.2	8.6	9.8	10.6	12.8	35.3	7.1	18.9	18.9	19.9
	Infusion	58.9	8.1	7.8	11.8	12.2	36.0	6.8	18.8	19.0	20.4
S. R.	Control	43.3	6.1	14.8	9.5	26.4	36.7	6.2	18.5	15.1	23.0
	Infusion	43.5	5.6	14.2	11.6	25.0	37.9	6.5	18.4	17.0	20.2
L. K.	Control	73.7	4.0	4.3	9.6	8.4	52.7	6.2	8.4	14.9	17.8
	Infusion	63.6	3.9	4.7	10.2	7.6	51.8	6.1	10.8	10.9	20.4
	Recovery	73.4	4.1	3.9	10.3	8.2	52.0	6.2	9.1	13.0	19.7
J. R.	Control	55.5	11.3	7.5	9.2	16.5	45.3	6.9	8.0	11.5	28.3
	Infusion	58.0	10.6	6.2	10.3	15.0	43.9	6.9	8.6	14.3	26.3
	Recovery	55.8	10.1	6.8	10.2	17.0	46.0	7.1	7.5	11.6	27.8

* All values were determined by paper electrophoresis and are expressed as percentages of the total urinary and serum proteins, respectively. *L*-norepinephrine or *l*-epinephrine was administered during the infusion period. The recovery periods were obtained immediately after cessation of the infusion of medullary hormones.

† α_1 plus α_2.

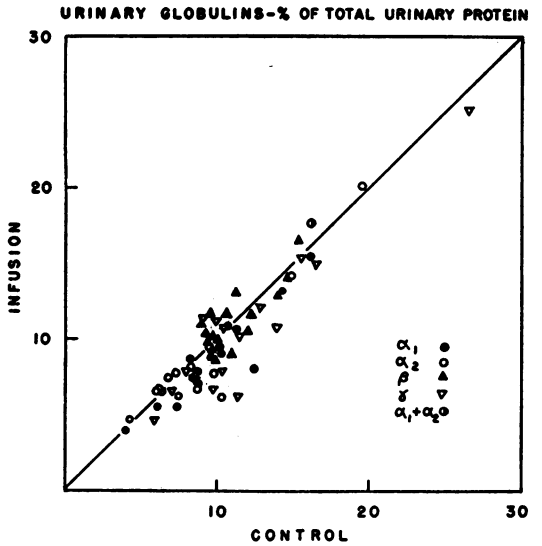

FIG. 3. URINARY GLOBULIN EXCRETION

The excretion of α_1, α_2, β, and γ globulin during the control periods, expressed as percentages of the total urinary protein, is plotted against the excretion of these fractions during the infusion of *l*-norepinephrine and *l*-epinephrine. Only those subjects in whom the protein-inulin clearance ratio increased are included. The relative proportions of the urinary globulins did not change during infusion of the pressor agents.

Systemic circulatory adjustments

There were no detectable changes in cardiac rate or arterial blood pressure during the administration of *l*-epinephrine. *L*-norepinephrine elicited adjustments similar to those reported previously in normal subjects (14). The systolic and diastolic blood pressures increased on the average 36 and 15 mm. Hg, respectively, and the cardiac rate diminished. On cessation of the infusion the blood pressure returned rapidly to control levels and the cardiac rate increased, often above control values.

Inulin and sodium p-aminohippurate (PAH) clearances

The averaged figures for inulin and PAH clearances during the control, infusion and recovery periods are tabulated in Table I and are arranged in a descending manner, according to the control inulin clearances. The changes elicited by *l*-norepinephrine and *l*-epinephrine were similar. The clearance of PAH diminished significantly in all but three subjects (E. B., J. B., and P. B.). On the average, PAH clearance decreased 23 per cent, with a range of 53 to 109 per cent of control values. The clearance of inulin remained constant in 12 subjects, decreased in 10 (12 to 61 per cent), and increased in 1 (E. B.). In subjects with severe renal functional impairment (W. E., J. H., O. B., and J. R.) the changes in the inulin clearance tended to be greater than in other subjects. The filtration fraction (C_{IN}/C_{PAH}) increased (10 per cent or more) in 16 subjects, decreased in 3 (J. B., O. B., and J. R.) and remained unchanged in four (E. B., J. H., J. M., and S. R.). During the recovery periods the clearances of inulin and PAH and the filtration fraction returned towards control values. PAH clearance exceeded control levels during recovery in 5 subjects (A. B., W. E., J. H., P. B., and J. R.). The clearance of inulin increased above control levels at this time in 3 subjects (A. B., W. C., and J. H.).

The similarity of these changes in renal clearances with those reported in normal subjects (14) suggests that the reduction in PAH clearance may be attributable, at least in part, to a reduced renal plasma flow. The associated reduction in the clearance of inulin and the rapid reversibility of the changes in PAH clearance support this view. Whether changes in the renal extraction of PAH also occurred was not established.

Urinary protein excretion

The effects of *l*-norepinephrine and *l*-epinephrine on urinary protein excretion ($U_{PR}V$, Table I) were similar. A variable response was observed. In 11 subjects (R. H., T. P., A. B., A. K.(A), J. O'B., T. D., P. L.(A), E. Z., W. E., A. K.(B), and P. L.(B)) the output of protein increased abruptly during the infusion of these agents. Protein output remained unchanged in 10 subjects and fell in 2 (O. B. and J. R.). Similar directional changes were observed in the clearance of protein, but since the concentration of serum proteins tended to rise, the magnitude of the alterations in protein clearance were less than those of protein excretion (C_{PR}, Table I). The mechanism of the rise in serum protein concentration is not clear but in view of the accompanying increment in the hematocrit of venous blood (Table I) this increase may be ascribed in part to hemoconcentration. A hemoconcentrating effect of epinephrine has been described previously (15).

A more consistent pattern of renal response was observed when the changes in protein clearance were related to changes in the inulin clearance. In 15 subjects the protein-inulin clearance ratio (C_{PR}/C_{IN}, Table I) increased during infusion of the adrenal medullary hormones (Figure 1). Thus, although protein excretion and clearance were unchanged in J. H. and S. R., and fell in O. B. and J. R., the protein-clearance ratio increased in all. In 8 subjects this ratio did not change. In three (J. B., E. B., and P. B.) of these subjects there were no associated adjustments of the renal circulation. Thus, in those instances in which renal vasoconstriction occurred, the protein-inulin clearance ratio increased in 15 and remained unchanged in 5. During the infusion the protein-inulin clearance ratio for the entire group of 23 subjects averaged 235 per cent of control values (range, 88 to 1146 per cent). This change was highly significant statistically ($t = 3.69$; $p < .01$). There was a significant correlation between the changes in this ratio and the changes in PAH clearance ($r = .565$; $p < .01$) (Figure 1). When the PAH clearance fell below 85 per cent of control values the clearance of protein increased relative to the inulin clearance (Figure 1). The changes in the protein-inulin clearance ratio could not be correlated with alterations in the inulin clearance or the filtration fraction since these parameters changed in a variable manner as protein output increased relative to filtration.

Following cessation of the infusion of the medullary hormones, the excretion and clearance of protein and the protein inulin-clearance ratio returned towards or to control values. In one subject (J. H.) protein excretion increased above the control level during recovery in association with renal hyperemia but the protein-inulin clearance ratio fell from the maximum value obtained during the pressor response to *l*-norepinephrine.

The relative proportions of the individual serum and urinary protein fractions did not change during the infusion of the medullary hormones or during recovery (Table II, Figures 2 and 3). In those subjects in whom the protein-inulin clearance ratio changed significantly during the infusion periods, there was no statistically significant change in the relative proportions of urinary albumin ($t = 1.93$; $p < .10 > .05$), α_1 globulin ($t = 1.17$, $p < .50 > .10$), α_2 globulin ($t = 2.53$; $p < .05 > .02$)[5], β globulin ($t = 1.21$; $p < .50 > .10$), or γ globulin ($t = 1.98$; $p < .10 > .05$).

DISCUSSION

The rate at which plasma proteins escape into glomerular filtrate in renal disease is governed by the characteristics of the protein molecules and by the structural and physiologic alterations in the glomerular membrane. The present study suggests that this process may be modified by the rate of blood flow through the kidney. When renal blood flow diminished as a result of the vasoconstrictive activity of the adrenal medullary hormones, *l*-norepinephrine and *l*-epinephrine, the rate of urinary excretion and renal clearance of plasma proteins increased abruptly. These alterations occurred independently of changes in systemic blood pressure and were not dependent upon but were influenced by changes in glomerular filtration rate. Thus, when the volume of filtrate diminished sharply as a result of intense renal vasoconstriction, as tended to occur in patients with severe renal functional impairment, less protein was available for excretion and the changes in protein output were not as apparent. However, the factors tending to accelerate the urinary loss of protein appeared to have been operative with equal force in these instances since the amount of protein excreted per unit of filtrate increased as it did when renal vasoconstriction was less intense and the changes in glomerular filtration rate were minimal (Figure 1).

These alterations in protein excretion may be attributed to either an increase in the transglomerular capillary transport of protein molecules or to a decrease in tubular reabsorption of protein, or to both. The present study did not distinguish between these possibilities. However, the similarity of the response in patients with renal disease with that observed in dogs in which the transglomerular transport of hemoglobin molecules increased during the pressor response to *l*-norepinephrine (10) suggests that the changes observed in the present study may be attributable, at least in part, to an accelerated transport of protein molecules across the glomerular membrane.

[5] This change was of borderline significance. In view of the small number of observations (14), statistical significance cannot be attached to this value.

Protein molecules apparently traverse capillary walls by both filtration and diffusion (2). The factors which govern the rates at which these processes occur are not entirely clear, but protein transport appears to depend, at least in part, upon the restricted area available for diffusion and upon a variety of physical factors which include the rate of hydrodynamic flow of fluid across the capillary wall and the thickness of the membrane through which flow occurs (2). According to the theory of molecular sieving the concentration of protein in capillary filtrates approaches that in the filtrand as the rate of transport of fluid across the membrane diminishes, owing to differences in the diffusion characteristics of protein and water molecules. This phenomenon has not been conclusively demonstrated in the kidney but has been suggested to account for the appearance of protein in the urine during circumstances in which momentary renal vasoconstriction occurs (2). However, this concept cannot account for the changes in protein output accompanying the renal vasoconstriction elicited in the present study by the adrenal medullary hormones since these changes occurred independently of alterations in glomerular filtration rate.

A more conventional explanation of the production or acceleration of proteinuria during renal vasoconstriction is that originally proposed in 1862 by Hermann (16) who suggested that these changes were brought about by an increase in capillary permeability secondary to anoxia. However, whether the dimensions of the channels through which the movement of protein molecules occurs are subject to variation under these and other experimental and physiologic conditions has not been clearly established. A change in pore size has been proposed to explain alterations in protein excretion not only during renal vasoconstriction but also under circumstances in which an increase in intraglomerular hydrostatic pressure was believed to have occurred, as during infusions of human serum albumin (3) and during the pressor response to renin (5).

Although these concepts must be considered in evaluating the changes in urinary protein excretion elicited by *l*-norepinephrine and *l*-epinephrine in the present study, certain evidence suggests that alterations in the size of the channels in the glomerular membrane secondary to either changes in intraglomerular hydrostatic pressure or to anoxia were not critical for the appearance of increased amounts of protein in the urine under the conditions of this study. Thus, protein output (or the protein-inulin clearance ratio) increased independently of changes in the renal filtration fraction, a parameter which may reflect corresponding adjustments of intraglomerular pressure provided the presence of vascular shunts within the kidney (17) does not invalidate interpretation of the filtration fraction in renal disease. Moreover, the observation that the clearances of the individual protein fractions increased equally in response to the medullary hormones (Figures 2 and 3) suggests that structural changes in the glomerular membrane secondary to an adjustment of glomerular capillary pressure or as a result of anoxia may not have been responsible since it appears unlikely that the transport of protein molecules of varying size and configuration would be equally affected by an increase in the dimensions of the channels through which this transport occurs. Furthermore, the rapid reversibility of the changes in protein output after cessation of the infusion of the medullary hormones tends to support the argument against structural alterations in the glomerular membrane, at least with respect to anoxia, since these alterations might have been expected to persist in part after the flow of blood through the kidney had been reestablished at or near its initial rate, thus prolonging the leakage of excess protein in the urine. This view would not apply, however, to an increase in the area available for diffusion brought about by adjustments of intraglomerular pressure since this change might be readily reversible as the hydrostatic pressure returned to control levels.

If these considerations suggest that the vasoconstrictive adjustments within the kidney did not affect protein output by altering the integrity of the glomerular membrane, they do not exclude the possibility that these adjustments altered protein output in some other manner. The correlation between protein clearance and the changes in PAH clearance (Figure 1) suggests that a reduction in the rate of blood flow through the kidney may have been responsible. The mechanism by which this circulatory adjustment may have acted is not clear. If under these conditions the rate and velocity of blood flow through the glomerulus diminished, the duration of contact between protein molecules and the capillary wall

may have been prolonged, thus allowing more time for the diffusion of these molecules into the glomerular filtrate. A similar hypothesis has been suggested to account for the increased excretion of hemoglobin in dogs during the pressor response to *l*-norepinephrine (10). Whether changes in the distribution of blood within the kidney (18) contributed to the results of the present study was not determined.

SUMMARY

A study was made of the effects of the adrenal medullary hormones, *l*-norepinephrine and *l*-epinephrine, on the urinary excretion and renal clearances of plasma proteins in 23 subjects with chronic renal disease and proteinuria. When these agents elicited moderate renal vasoconstriction the clearances of plasma protein increased abruptly. When the amount of filtrate was greatly reduced as a result of more intense vasoconstriction, the changes in protein excretion and clearance were less marked, although protein output increased relative to filtration, suggesting that the forces tending to accelerate protein excretion were operative in these instances as well.

These changes, which involved the individual protein fractions equally, occurred independently of alterations in systemic blood pressure, glomerular filtration rate and the renal filtration fraction, but were not observed in the absence of renal vasoconstriction and a reduction in renal plasma flow. The mechanisms responsible for altering protein output under these conditions were not determined. Although changes in tubular protein reabsorption and anoxic alteration of the glomerular membrane could not be excluded, it was suggested that the observed changes in protein output were attributable to an increased rate of diffusion of protein molecules into the glomerular filtrate owing to a more prolonged contact between these molecules and the capillary wall as a result of the slowing of blood flow through the glomerulus.

ACKNOWLEDGMENT

The author is indebted to Miss Marion Brazel and Mrs. Frances Kennedy for technical assistance.

REFERENCES

1. Lathem, W., Intrarenal hemodynamic adjustments and urinary protein excretion in patients with renal disease. Clin. Res. Proc., 1956, **4**, 141.
2. Pappenheimer, J. R., Passage of molecules through capillary walls. Physiol. Rev., 1953, **33**, 387.
3. Chinard, F. P., Lauson, H. D., Eder, H. A., Greif, R. L., and Hiller, A., A study of the mechanism of proteinuria in patients with the nephrotic syndrome. J. Clin. Invest., 1954, **33**, 621.
4. Davson, H., and Danielli, J. F., The Permeability of Natural Membranes. Cambridge, England, The University Press, 1943.
5. Addis, T., Barrett, E., Boyd, R. I., and Ureen, H. J., Renin proteinuria in the rat. I. The relation between the proteinuria and the pressor effect of renin. J. Exper. Med., 1949, **89**, 131.
6. Lathem, W., Roof., B. S., Nickel, J. F., and Bradley, S. E., Urinary protein excretion and renal hemodynamic adjustments during orthostasis in patients with acute and chronic renal diseases. J. Clin. Invest., 1954, **33**, 1457.
7. Starr, I., Jr., The production of albuminuria by renal vasoconstriction in animals and in man. J. Exper. Med., 1926, **43**, 31.
8. Chesley, L. C., Markowitz, I., and Wetchler, B. B., Proteinuria following momentary vascular constriction. J. Clin. Invest., 1939, **18**, 51.
9. King, S. E., and Baldwin, D. S., Production of renal ischemia and proteinuria in man by the adrenal medullary hormones. Am. J. Med., 1956, **20**, 217.
10. Lathem, W., and Benjamin, A. D., Intrarenal circulatory dynamics and urinary hemoglobin excretion during infusions of l-norepinephrine in dogs. In preparation.
11. Goldring, W., and Chasis, H., Hypertension and Hypertensive Disease. New York, The Commonwealth Fund, 1944.
12. Hiller, A., Greif, R. L., and Beckman, W. W., Determination of protein in urine by the biuret method. J. Biol. Chem., 1948, **176**, 1421.
13. Böger, A., and Wezler, K., Die Bestimmung des arteriellen Gesamtwiderstandes am Menschen. Arch. f. exper. Path. u. Pharmakol., 1937, **186**, 43.
14. 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.
15. Edmunds, C. W., and Nelson, E. E., Factors concerned in the polycythemia produced by the subcutaneous injection of epinephrine. J. Exper. Med., 1925, **41**, 1.
16. Hermann, M., Quoted in Starr, I., Jr. (7).
17. Oliver, J., Architecture of the Kidney in Chronic Bright's Disease. New York, P. B. Hoeber, Inc., 1939.
18. Pappenheimer, J. R., and Kinter, W. B., Unequal distribution of red cells and plasma in renal cortex; significance for renal hemodynamics. Federation Proc., 1955, **14**, 110.