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Research Article

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Function of the Nephron Population during Hemorrhagic Hypotension in the Dog, with Special Reference to the Effects of Osmotic Diuresis *

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The composition of the kidney as a complex of nephrons, each concerned independently in processing the glomerular filtate, seriously complicates the interpretation of changes in urine formation in terms of nephron behavior. To reach any conclusions regarding individual nephron function, all nephrons must be assumed to be alike and to act in the same manner. All the nephrons in the kidneys of the dog and man are indeed similarly constructed, but they do vary widely in over-all measurements and proportionalities (1–3). To some extent, the functional heterogeneity implicit in this dimensional variance is minimized by the combination of glomeruli and proximal convoluted tubules of comparable size in such a way as to match filtered load with tubular capacity (3, 4). Even so, however, functional uniformity must hinge upon a predictable and regular supply of glomerular filtrate to the tubules. Since filtration is a hemodynamic process, circulatory adjustment might impose a further nonuniformity of intracortical perfusion, perhaps resembling that already evident at rest in the distribution of blood to the medulla and cortex (5). That the renal pathology of circulatory collapse is most pronounced in the cortex (6, 7) chimes in with this possibility by suggesting that the cortical nephrons may be particularly vulnerable, perhaps because they lie on the periphery of the renal vasculature where vascular pressures might be most affected by arterial hypotension. If this inference is justifiable, disparities in nephron function arising from extrinsic causes as well as from inherent structural differences must be allowed for.

To determine if arterial hypotension may affect some nephrons preferentially, a study of glomerular and tubular activity was made in dogs after controlled blood loss. In measuring maximal tubular reabsorption of glucose as a guide to changes in nephron population, a profound osmotic diuresis was produced that made possible not only the marking out of changes in distal tubular concentrating mechanisms more precisely, but also, quite incidentally, the obtaining of evidence that under certain circumstances glomerular filtration may persist in the absence of urine formation. The data indicate that filtration does decrease in proportion to arterial pressure, presumably after a maximal autoregulatory adjustment has occurred, but that maximal tubular transport capacity falls only after lower blood pressures are reached and, even then, less than filtration at each successively lower level. The nephron population appears to be functionally heterogeneous, therefore, at least with respect to the distribution of effective glomerular filtration pressures. The imposition of a uniformly distributed critical arterial pressure change under these circumstances might be expected to result in the cessation of filtration in some units but also in diminution in all those remaining in operation.

Methods

Measurements of glomerular and tubular function were made on 42 occasions before and during the maintenance of a steady hypotensive state produced by graded hemorrhage in 32 healthy, fasting, well-hydrated, mongrel bitches, ranging in body weight from 8 to 22 kg.

Experimental procedure. Anesthesia was induced at the outset of each study by pentobarbital sodium in an initial dose of 30 mg per kg (6% Nembutal), given intravenously via a foreleg vein and maintained thereafter

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TABLE I

*Effect of hemorrhagic hypotension on tubular transfer maxima**

Dog	Wt	Period	Hct	BP	V	C_{In}	SD	P_G	U_GV	Tm_G	SD	P_D	Tm_D	SD	L/Tm_G
	kg		%	*mm Hg*	*ml/min*	*ml/min*		*mg/100 ml*	*mg/min*	*mg/min*		*mg/100 ml*	*mg I_2/min*		
Belinda	21	C	50	135	5.0	75.2	±3.3					45	14.1	±0.6	
		H	40	90	5.0	63.8	±3.7					66	11.9	±1.4	
		H	38	78	5.0	50.6	±5.0					70	13.8	±3.1	
		H	37	65	4.2	36.9	±0.35					82	10.4	±4.5	
Cupid I	16	C	41	118	3.6	67.2	±2.1					33	8.0	±0.8	
		H	36	74	1.3	65.6	±7.6					31	7.7	±1.3	
Cupid II	16	C	29	115	6.2	68.5	±5.2					30	9.8	±1.4	
		H	29	63	0.8	52.7	±1.2					33	8.8	±3.0	
		H	26	60	1.2	30.2	±5.6					33	5.6	±1.3	
Dasha I	15	C	40	105	4.8	57.9	±3.7					32	6.0	±1.0	
		H	35	63	0.5	29.5	±3.5					38	4.5	±1.0	
Dasha II	15	C	42	111	0.8	63.1	±6.8					20	10.3	±2.1	
		H	34	57	0.3	50.1	±2.7					13	9.7	±1.4	
Emily I	9	C		110	3.6	37.3	±2.3	660	174	71	±17	34	9.0	±1.4	3.5
		H		60	3.7	20.3	±0.7	1,300	193	66	±15	41	7.4	±1.5	3.6
Florence	13	C	47	130	5.8	39.9	±8.2	970	270	116	±32	27	5.2	±0.7	3.3
		H	39	42	6.3	20.5	±3.2	1,170	147	92	±26	29	5.2	±0.5	2.0
Emily II	9	C	34	111	6.6	39.3	±1.5	940	254	110	±5				3.3
		H	40	68	0.6	18.4	±1.1	800	41	104	±7				1.3
Gloria I	9	C	43	115	4.7	46.3	±4.9	390	30	112	±13				1.6
		H	32	65	0.7	22.5	±2.2	730	32	122	±12				1.2
Hazel	18	C	40	110	4.9	55.1	±4.1	870	297	183	±35				2.6
		H	36	58	1.4	36.0	±5.0	790	100	182	±35				1.6
Gloria II	9	C	35	125	4.6	55.0	±3.1	840	256	206	±29	22	10.8	±1.2	2.3
		H	25	44	1.1	10.9	±0.9	1,430	71	86	±13	26	4.5	±0.7	0.8
		H	25	37	0.7	5.6	±1.4	1,600	44	45	±19	34	4.3	±1.2	0.4
Irma	12	C	35	108	5.7	74.0	±4.3	611	208	238	±25	32	6.3	±1.8	1.9
		H	20	42	1.0	15.0	±1.4	1,217	100	171	±8	40	3.4	±0.8	1.2
Jackie	17	C	39	106	3.2	78.1	±6.3	500	177	215	±29	29	11.0	±2.1	1.9
		H	31	38	1.8	30.4	±2.0	980	140	164	±20	31	9.6	±1.5	1.4
		H	30	33	1.6	21.8	±2.5	1,180	128	130	±3	32	8.1	±0.5	1.3
Karla I	22	C	42	135	4.0	82.9	±6.1					27	16.4	±2.0	
		H	40	48	3.3	38.0	±7.1					29	10.1	±1.0	
		H	38	45	2.0	21.7	±0.4					31	9.8	±0.2	
		H	36	45	1.7	17.9	±0.6					34	9.4	±0.4	
Morena	12	C	46	114	8.5	40.3	±3.1					48	9.3	±1.1	
		H	33	43	1.6	9.0	±1.9					52	4.5	±0.3	
		H	25	41	1.4	4.6	±0.9					59	4.1	±0.4	
Leonia	14	C	42	124	6.5	54.1	±4.5	700	270	106	±25	38	10.1	±3.6	3.5
		H	22	44	1.7	4.5	±2.2	3,400	83	40	±30	60	0.6	±0.4	1.4
Karla II	22	C	32	120	4.1	81.0	±7.8	600	244	239	±13	30	23.5	±1.3	2.0
		H	23	47	4.1	30.0	±3.4	1,590	279	197	±20	26	14.2	±1.2	2.0
Ortrude I	12	C		120	2.5	41.7	±5.7	760	171	146	±20	35	12.8	±1.9	2.2
		H		68	4.5	40.0	±3.2	1,100	302	141	±28	22	12.8	±0.6	3.1
Ortrude II	12	C	26	152	2.5	59.7	±4.8	510	144	162	±24	23	16.7	±1.4	1.9
		H	20	50	1.2	9.1	±2.0	1,710	74	81	±17	26	5.2	±1.1	1.0
		H	17	50	0.8	4.9	±0.1	2,070	45	55	±5	29	2.9	±0.3	0.6
		H	15	50	0.6	2.1	±0.7	2,430	30	20	±10	34	1.2	±0.6	0.3
Gloria III	9	C	42	122	4.3	46.0	±5.3	550	133	117	±25	29	9.1	±1.0	2.2
		H		63	2.0	20.4	±0.5	1,220	130	119	±4	35	6.3	±2.7	2.2
		H		61	1.8	15.5	±1.0	1,310	119	85	±15	33	5.0	±1.1	1.7

* Each datum is an average of three or more values obtained consecutively during the periods of control (C) and hemorrhagic hypotension (H) for the hematocrit (Hct), arterial pressure (BP), urine flow (V), inulin clearance (C_{In}), arterial plasma concentrations of glucose (P_G) and Diodrast (P_D), and urinary output of glucose (U_GV). The filtered load of glucose (L/Tm_G) imposed upon the tubules for reabsorption was computed in each instance by dividing the average value for filtered glucose in each period by the control Tm_G. To indicate variation succinctly, the standard deviations (SD) were computed for C_{In}, Tm_G, and Tm_D.

by constant iv infusion at a rate sufficient to abolish the corneal reflex, usually 0.03 mg per minute per kg body weight (range, 0.02 to 0.04). The body temperature was sustained throughout by an electric heating pad. To assure adequate hydration and urine flow, 200 to 400 ml of warm tap water was given by gastric tube to some of the animals as soon as anesthesia was induced. In others, the same amount of 0.45 or 0.90% NaCl solution was given by the vein employed for the continuous administration of pentobarbital. An indwelling plastic catheter was affixed in a femoral artery to permit continuous measurement of the mean arterial pressure by mercury manometer. A three-way stopcock in the connecting tubing permitted sampling arterial blood and taking off measured quantities of blood into a sterile receiving bottle.

The maximal tubular transfer capacities for glucose (Tm_G) and Diodrast (Tm_D, iodopyracet), or both, and the glomerular filtration rate (inulin clearance, C_{In}) (8) were measured in 20 studies of 13 dogs (Table I). The plasma levels of these substances were maintained relatively constant (between 14 and 80 mg per 100 ml for inulin, in excess of 20 mg iodine per 100 ml for Diodrast, and greater than 400 mg per 100 ml for glucose) by constant infusion of solutions made up in appropriate concentrations in sterile distilled water. At the end of three or four control periods (8 to 13 minutes), a single dose of 3,000 to 5,000 μg of heparin was given intravenously, and blood was then withdrawn rapidly until the blood pressure had fallen to about 70 mm Hg. At this point, the blood pressure usually showed a tendency to rise towards the control values when bleeding was stopped. Hence, bleeding was continued cautiously until the desired level of blood pressure was reached and all detectable tendency to return to control values eliminated. The final pressure level was chosen for each experiment to assure a fall to approximately 50% of the control value, with due consideration for individual tolerance and the establishment of a regular, rapid pulse, stable arterial pressure, and a significant but not excessive reduction in urine flow.

The infusion rate of test substances was reduced after hemorrhage to prevent an excessive rise in plasma levels as a result of decreased renal excretion. To assure adequate glucose loading of the tubules in the last six studies (Table I), the plasma glucose concentration was increased during the period of hypotension by the administration of a second priming dose at the time of the bleeding and addition of glucose (50%) to the infusion. The time between the onset of blood loss and completion of the study (3 to 7 periods) averaged 140 minutes, ranging from 105 to 180 minutes. The blood was reinfused at the end of each experiment, with complete recovery of 5 animals in whom the study could be repeated a second time 1 week or more later. In one (Gloria) the carotid artery and jugular vein were used in the course of a third experiment. Urine and plasma samples in the first group of 20 studies were analyzed only for inulin, glucose, and Diodrast.

Twenty-two similar experiments were performed in 19 dogs for the purpose of studying water and electrolyte excretion under the same conditions (Table II). Pitressin (vasopressin) was given by infusion (8 mU per minute) in all studies but one (Wilhelmina I). After two control periods, the blood pressure was first adjusted at or above 48% of control by bleeding, and four periods were collected. A second bleeding brought the arterial pressure down to a lower level, at which four more periods were collected. Although Diodrast was given to assure comparability with the first group of animals, it was not determined analytically. All urine and plasma samples were analyzed for inulin, glucose, sodium, potassium, and osmolality. To avoid errors in the determination of urinary osmolality, only air was used to assure emptying of the bladder. The marked hyponatremia observed in the six initial studies (Wilhelmina I to Amalia, Table II) was corrected thereafter by adding 0.9% sodium chloride instead of distilled water to the sustaining infusion.

Analytical methods. Hematocrit determinations were made by spinning blood in Wintrobe tubes for $\frac{1}{2}$ hour at 3,000 rpm.

Plasma proteins were precipitated with cadmium sulphate and sodium hydroxide in the first five studies and with balanced zinc sulphate and barium hydroxide in the remainder (8). A slightly acid filtrate did not affect the glucose and Diodrast determinations and was found preferable for the adequate recovery of inulin. This was accomplished with a zinc sulphate reagent prepared to produce a faint pink color with phenolphthalein on titration with 2.2 ml of barium hydroxide, of which only 2.0 ml were then used for the precipitation. Inulin was determined by the Harrison method, as modified by Smith (8). Since glucose concentrations were high in these experiments, 6 ml of a 30% yeast suspension was mixed with 2 ml of plasma or 1:10 urine dilution, agitating every 5 minutes during 30 to 45 minutes.

Glucostat reagent[1] was used for the enzymatic determination of glucose in plasma and urine (9). The reagent containing Glucostat and Chromogen (o-dianisidine) was made up to a final volume of 100 ml. Urines were diluted 1,000- to 2,500-fold according to the estimated glucose concentrations, and the final dilution was adsorbed with Lloyd reagent (hydrated aluminum silicate) in the proportion of 5 g of Lloyd reagent per 20-ml sample of diluted urine. When treated in this fashion, recoveries of glucose from urine samples were within $100 \pm 3\%$. The reaction was carried out by mixing 8 ml of reagent with 2 ml of the adsorbed urine samples or diluted plasma filtrates, incubating for 30 minutes in a water bath at 37° C, and stopping the color development with 1 ml of 0.5 N H_2SO_4. Three standards containing 1, 2.5, and 4 mg per 100 ml glucose in aqueous solution and 2 ml of distilled water (reagent blank) were added directly to the reagent and incubated with the samples. Standards and samples were then read against the reagent blank in a Coleman Universal

[1] Worthington Biochemical Corp., Freehold, N. J.

TABLE II

*Effect of hemorrhagic hypotension upon renal excretion of electrolytes and water**

Dog	Wt	Period	Hct	BP	V	C_{In}	±SD	C_{In}/Tm_G	Tm_G	±SD	L/Tm_G	U/P_{osm}	$T^c_{H_2O}$	U_GV	C_{Na}/C_{In}	C_K/C_{In}	P_G	P_{Na}	P_K
	kg		%	*mm Hg*	*ml/min*	*ml/min*			*mg/min*				*ml/min*	*mg/min*			*mg/100 ml*	*mEq/L*	*mEq/L*
Wilhelmina I	14	C		100	6.9	53.3	±0.35	34.2	156	±5.66	3.3	1.43	2.95	364	5.65	27.3	970	137	3.7
		H	37	71	2.6	41.2	±2.35	25.9	159	±9.60	2.3	1.66	1.70	197	0.61	20.0	870	137	3.5
		H	37	52	2.1	37.1	±1.82	28.8	129	±11.70	1.9	1.74	1.53	163	0.14	23.8	790	137	3.4
Xanthine I	9	C	36	122	12.1	52.9	±0.99	35.7	148	±5.66	3.2	1.15	1.73	327	14.05	46.4	900	142	3.7
		H	27	77	1.2	20.4	±3.85	14.7	139	±24.30	1.4	1.55	0.65	68	0.07	25.1	1,030	129	3.4
		H	18	53	1.0	10.7	±3.75	11.0	97	±39.10	1.0	1.34	0.32	53	0.12	22.9	1,370	115	3.7
Wilhelmina II	14	C	35	111	11.6	53.0	±1.55	36.1	147	±45.30	4.9	1.22	2.55	563	11.05	54.2	1,340	131	4.6
		H	29	68	6.3	30.8	±1.20	34.6	89	±14.80	3.7	1.27	1.67	454	1.17	42.0	1,760	128	4.2
		H	24	49	4.2	23.0	±1.99	24.5	94	±8.89	2.8	1.33	1.37	314	0.16	30.7	1,780	130	3.8
Xanthine II	9	C	22	109	8.1	38.5	±3.47	22.2	139		3.5	1.20	1.60	353	11.50	30.5	1,150	128	3.4
		H	24	55	2.8	26.7	±3.10	17.5	152	±15.00	2.5	1.38	1.06	194	0.15	20.2	1,300	129	2.9
		H	17	40	1.1	12.1	±0.92	10.0	121	±18.80	1.3	1.33	0.35	70	0.04	17.6	1,580	122	2.9
Yolanda	11	C	27	125	13.2	48.4	±1.84	35.3	137	±6.37	4.7	1.09	1.20	506	12.70	45.6	1,300	128	3.8
		H	24	71	6.6	27.4	±1.18	29.1	94	±7.09	3.8	1.24	1.46	426	1.77	37.5	1,890	120	3.0
		H	20	49	3.1	12.1	±0.85	16.6	73	±3.54	2.1	1.22	0.61	219	0.10	23.6	2,300	121	2.3
Amalia	12	C	22	125	10.4	34.6	±1.13	34.3	101	±5.66	6.6	1.14	1.46	562	8.03	39.5	1,900	122	3.8
		H	19	70	4.3	13.8	±1.43	23.4	59	±13.60	4.0	1.26	1.12	336	0.71	47.7	2,820	113	3.6
		H	15	46	1.2	4.4	±1.72	9.1	48	±13.40	1.4	1.22	0.28	94	0.91	24.0	3,530	109	2.9
Carmen I	10	C	33	130	15.4	52.3	±2.50	29.7	176	±20.00	3.7	1.17	2.60	480	18.80	50.4	1,260	140	3.6
		H	30	86	5.3	39.4	±2.50	26.3	150	±22.00	2.3	1.51	2.69	259	6.59	44.3	1,170	151	3.5
		H	25	55	1.6	15.0	±0.70	9.9	152	±5.00	1.5	1.53	0.81	106	0.20	28.1	1,990	143	2.7
		H	20	60	1.8	11.1	±0.10	11.4	97	±7.00	1.2	1.43	0.74	123	0.10	30.2	1,990	137	2.4
Dalilah	10	C	36	145	15.6	45.8	±1.10	23.5	195	±10.00	3.6	1.08	1.27	549	21.50	59.4	1,620	157	4.0
		H	33	69	3.6	22.8	±2.70	16.5	138	±20.00	2.1	1.41	1.47	277	3.14	28.7	1,830	157	3.5
		H	28	53	1.1	8.2	±1.20	8.6	95	±10.00	1.0	1.35	0.40	93	1.37	21.6	2,280	153	2.7
		H	22	50	2.5	6.7	±2.00	9.7	69	±16.00	1.0	1.10	0.37	130	22.24	61.7	3,020	147	4.0
Carmen II	10	C	33	125	14.8	46.8	±4.20	31.6	148	±3.00	4.6	1.18	1.92	529	18.50	152.4	1,450	140	3.6
		H	24	70	3.8	24.8	±1.50	21.8	114	±4.00	2.6	1.49	1.69	272	2.70	26.5	1,560	143	2.6
		H	18	51	2.1	11.4	±1.30	17.0	67	±4.00	1.6	1.36	0.77	165	1.14	12.4	2,060	138	2.6
Elvira	14	C	35	160	15.9	60.6	±1.30	38.6	157	±5.00	5.5	1.23	3.70	701	13.90	39.8	1,420	140	3.9
		H	22	77	3.9	22.6	±2.90	13.3	170	±48.00	3.0	1.39	1.52	302	0.37	28.5	2,090	134	2.5
		H	18	54	1.6	8.8	±0.50	9.2	96	±10.00	1.3	1.26	0.41	114	0.13	19.2	2,400	131	2.5
		H	14	53	2.1	9.5	±1.20	10.1	94	±15.00	1.6	1.23	0.50	154	0.45	20.8	2,630	139	2.6

* Data and abbreviations as in Table I. The average values for inulin clearance relative to Tm_G (C_{In}/Tm_G), the urinary plasma osmolality ratio (U/P_{osm}), reabsorption of solute-free water ($T^c_{H_2O}$), the fraction of filtered sodium (C_{Na}/C_{In}) and filtered potassium (C_K/C_{In}) excreted in the urine, and plasma concentrations of sodium (P_{Na}) and potassium (P_K) have been added.

TABLE II—*Continued*

Dog	Wt	Period	Hct	BP	V	C_{In}	±SD	C_{In}/Tm_G	Tm_G	±SD	L/Tm_G	U/P_{osm}	$T^c_{H_2O}$	U_GV	C_{Na}/C_{In}	C_K/C_{In}	P_G	P_{Na}	P_K
	kg		%	*mm Hg*	*ml/min*	*ml/min*			*mg/min*				*ml/min*	*mg/min*			*mg/100 ml*	*mEq/L*	*mEq/L*
Frances	15	C	33	149	21.0	55.6	±0.10	42.4	131		6.1	1.05	1.00	710	21.40	62.1	1,440	133	3.5
		H	28	79	5.9	31.3	±3.00	25.2	124	±28.00	3.7	1.31	1.84	394	2.53	38.3	1,510	138	3.3
		H	26	56	2.6	16.0	±2.20	14.3	112	±4.00	2.3	1.25	0.67	183	0.12	18.3	1,850	138	2.4
Germaine	12	C	33	120	14.3	45.7	±3.20	39.4	116	±4.00	6.4	1.16	2.24	632	15.80	75.6	1,640	134	4.7
		H	36	92	7.0	26.2	±1.60	21.8	120	±29.00	5.1	1.28	1.92	475	6.06	53.2	2,270	135	4.2
		H	33	55	3.0	13.1	±2.00	16.2	81	±12.00	2.8	1.32	0.94	242	1.95	38.0	2,470	138	4.2
Hilda	11	C	30	140	13.6	49.5		51.0	97		6.7	1.13	1.84	540	17.60	40.2	1,360	133	3.3
		H	22	82	3.4	20.6	±2.00	20.6	100	±16.00	3.5	1.29	1.00	246	1.08	25.0	1,680	136	4.2
		H	15	52	2.0	9.2	±0.50	13.7	67	±14.00	2.1	1.18	0.36	146	0.22	14.3	2,320	132	4.6
Irene	11	C	37	160	15.5	44.4	±0.20	38.9	114	±34.00	6.4	1.06	0.98	610	17.20	60.3	1,640	138	4.4
		H	22	80	3.5	17.0	±1.70	16.0	106	±33.00	3.2	1.30	1.06	261	0.26	37.1	2,160	134	4.8
		H	21	72	2.0	9.2	±1.00	13.8	67	±2.00	2.0	1.28	0.58	158	0.22	23.2	2,450	133	3.7
		H	20	65	1.6	6.6	±0.30	14.4	46	±7.00	1.6	1.16	0.25	127	1.57	24.8	2,620	135	3.7
Joselyn	14	C	31	145	13.5	50.4	±0.60	54.0	93		7.7	1.28	3.80	660	12.95	47.7	1,460	139	4.0
		H	30	94	5.1	28.6	±2.10	27.7	103	±18.00	5.7	1.48	2.42	424	1.69	29.0	1,840	136	3.9
		H	30	60	2.2	13.2	±1.70	12.2	108	±14.00	3.2	1.43	0.97	193	0.25	19.3	2,280	133	3.7
Katrina	9	C	26	160	9.4	30.3	±0.20	44.3	68.4	±19.20	7.0	1.20	1.83	415	10.59	54.0	1,600	188	4.7
		H	21	90	4.2	17.0	±3.20	38.3	44.4	±4.80	5.0	1.34	1.43	297	3.98	28.2	2,020	180	3.3
		H	19	70	0.9	2.0	±0.80	20.5	9.9	±3.95	1.0	1.09	0.05	47	14.72	58.9	2,780	167	2.6
Melissa	14	C	30	115	22.8	54.7	±1.30	58.2	94	±4.00	10.5	1.08	1.70	887	23.10	81.2	1,790	132	3.9
		H	36	87	5.6	24.3	±3.10	28.6	85	±11.00	5.3	1.35	1.94	410	4.31	35.0	2,050	136	3.2
		H		55	2.0	6.6	±0.69	13.2	50	±12.00	2.2	1.26	0.59	161	1.07	23.0	3,220	133	3.2
Natalie	9	C	32	105	12.8	58.9	±3.10	42.7	138	±26.00	4.4	1.18	2.26	471	13.50	45.8	1,040	142	3.0
		H	35	88	8.4	51.6	±3.60	34.9	148	±8.00	4.6	1.37	3.06	484	6.68	41.4	1,230	145	3.2
		H	28	50	2.9	24.1	±3.30	19.0	127	±33.00	2.8	1.48	1.40	257	0.13	22.2	1,590	146	2.6
Olivia	7	C	31	100	14.1	60.2	±0.90	39.9	151	±20.00	4.2	1.07	0.98	487	13.10	33.3	1,060	141	3.4
		H	29	73	6.2	47.2	±1.90	34.2	138	±16.00	3.4	1.35	2.14	372	4.37	29.9	1,080	147	3.4
		H	24	40	0.8	6.0	±0.96	24.0	25	±7.00	0.5	1.23	0.18	50	0.17	46.7	1,210	148	3.1
Polka	14	C	38	135	14.0	62.5	±0.10	34.2	183	±35.00	5.0	1.30	4.15	743	10.20	39.0	1,480	132	4.0
		H	35	87	5.6	32.2	±2.90	29.5	109	±13.00	3.1	1.46	2.58	457	1.80	37.7	1,780	133	3.0
		H	22	47	0.5	3.1	±0.77	6.3	50	±19.00	0.5	1.15	0.07	34	0.25	20.1	2,640	122	2.6
Quincy	16	C	26	130	15.7	64.1	±2.00	51.7	124		7.7	1.30	4.61	838	11.20	52.3	1,480	133	4.4
		H	27	72	5.6	39.5	±4.40	27.2	145	±16.00	4.9	1.48	2.70	460	0.88	30.7	1,540	138	3.7
		H	30	50	1.5	13.4	±3.10	9.7	139	±31.00	2.1	1.36	0.56	118	0.15	23.4	1,950	133	2.7
Roberta	12	C	34	130	15.2	55.6	±3.30	35.0	159	±59.00	4.0	1.12	1.81	477	17.70	68.4	1,140	136	3.4
		H	34	71	5.5	32.6	±0.90	28.4	115	±19.00	3.1	1.36	1.94	377	2.70	28.0	1,510	135	2.7
		H	27	40	1.9	12.3	±1.20	16.8	73	±11.00	1.4	1.38	0.74	149	0.13	19.0	1,810	132	2.4
		H		40	1.5	7.8	±1.40	17.7	44	±10.00	1.0	1.33	0.50	110	0.12	25.1	1,970	131	2.2

spectrophotometer at 400 mμ. Diodrast was used rather than sodium *p*-aminohippurate (PAH) to avoid the possibility of glucose-PAH interaction (10) and depression of PAH Tm by glucose (11). Diodrast was determined by the method of Alpert as modified by Smith (8). Sodium and potassium were measured in fractions of appropriate dilutions of urine and serum by flame photometry; osmolality, by freezing point depression using a Fiske osmometer.

Results

Glomerular filtration rate. The control values (Tables I and II) for C_{In} in 32 dogs averaged 4.28 ± 1.17 ml per minute per kg body weight with an average arterial pressure of 125 ± 17 mm Hg. After hemorrhage, C_{In} and arterial pressure decreased together (Figure 1). Statistical analysis indicated close correlation between the two (r = 0.81), and the linear regression line (Figure 1) intersected with the x-axis at a value for arterial pressure equal to 22% of the control. The tendency observed by other investigators (12, 13) for glomerular filtration rate (GFR) to be sustained over a wide range of arterial pressure was not encountered, presumably because arterial pressure nearly always fell to levels below those at which the reported regulation occurs. In most animals the arterial pressure fell below 80 mm Hg after hemorrhage, but even in nine studies in which the arterial pressures after the initial bleeding were between 80 and 95 mm Hg, all but two figures for GFR were less than 80% of control. On two occasions GFR remained close to the control levels when arterial pressure fell below 75 mm Hg, or less than 65% of the control figures. Data from 14 animals not receiving Pitressin did not differ significantly on statistical analysis at each arterial pressure level from those obtained in studies in which Pitressin was infused throughout. In Figure 1 each datum is presented in terms of its control value so that the scatter about the regression line is less than that evinced by the absolute figures. Glomerular filtration was always measurable when arterial pressure was maintained in excess of 30 mm Hg or 30% of the control (Figure 1). In the absence of values for plasma protein concentration, calculations of plasma oncotic pressure could not be made, but the inference may be drawn that with such a correction the point of intersection of the regression line with the base would closely approach the origin. Within the range of arterial pressures observed in this study after hemorrhage, GFR appeared, therefore, to fall chiefly as a result of the fall in arterial pressure without evidence of associated changes in intrarenal vascular resistances. Whatever curvilinearity that might have been introduced by such a response seems to have been of minor significance. Perhaps reactive adjustments occurred as the pressure fell to 60 or 70% of control and became constant thereafter.

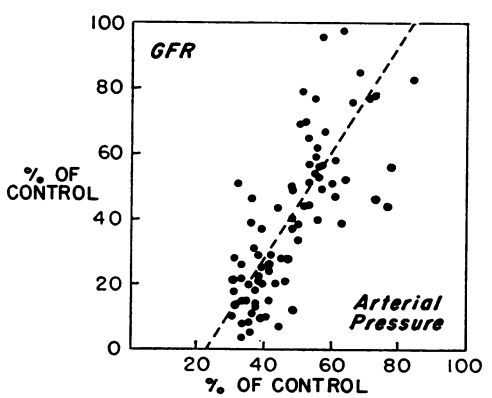

FIG. 1. RELATIONSHIP BETWEEN GLOMERULAR FILTRATION RATE (GFR) AND MEAN ARTERIAL PRESSURE AFTER HEMORRHAGE. Each datum is the mean of two or more successive determinations, expressed as percentage of the control value in each study (Tables I and II). The figures fall about the dashed regression line (y = −36.3 + 1.63x, r = 0.81).

Maximal tubular transfer rates. The maximal rate of glucose reabsorption by the tubules (Tm_G) averaged 11.47 ± 4.33 mg per minute per kg body weight in 28 dogs (Tables I and II) during the control periods. Glomerular filtration rate decreased after hemorrhage independently of Tm_G down to levels as low as 60% or less of control (Figure 2), corresponding to arterial pressures at or below 75 mm Hg or 50 to 60% of control. As GFR fell further, Tm_G also decreased but, in the great majority of studies, to a somewhat lesser extent, so that the GFR/Tm_G ratio presumably implies a reduction in the filtered load imposed upon each residual nephron active in producing urine. The apparent reduction in functioning nephron population responsible for the fall in Tm_G might be expected, per se, to affect urine secretion if the elimination of nephrons did not occur randomly or if the nephrons remaining in operation reabsorbed electrolytes and water in a manner

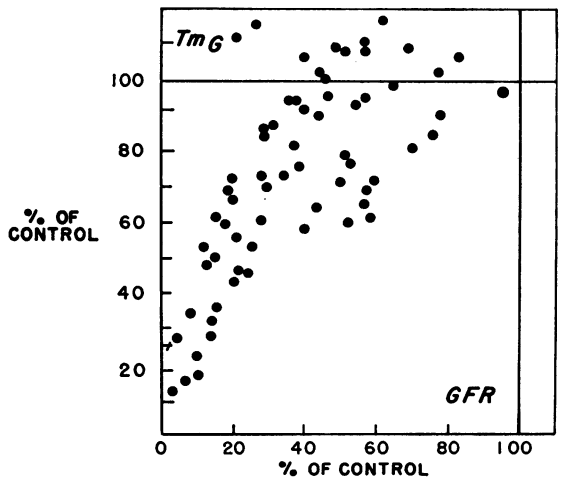

FIG. 2. RELATIONSHIP BETWEEN MAXIMAL RATE OF TUBULAR GLUCOSE REABSORPTION (T_{MG}) AND GFR AFTER HEMORRHAGE. The data show a tendency for Tm_G to be maintained until GFR has fallen below 60% of control in each study.

differing from that characteristic of those no longer in operation. Before any such conclusion would be warranted, however, the validity of the measurement of Tm_G as a measure of the active nephron population must be evaluated.

Perhaps the most serious difficulty in using the measurement of maximal transfer rate of any substance as a means of estimating nephron mass springs from uncertainty regarding the adequacy to saturate the transporting systems of the loads imposed for transfer. Constancy of the values for Tm over a wide range of blood levels is a reasonable basis for believing that the mass of functioning tubular tissue is constant. With a decrease, however, doubt must always arise as to whether the change is to be ascribed to diminution in the functioning cell mass, to change in cellular function, or to a reduction in load below the saturation level. In our study, for example, the described decrease in Tm_G might have resulted from the fall in GFR and in the filtered load of glucose to values less than those required for maximal transfer. To forestall this possibility, the plasma glucose concentration was maintained throughout at an extremely high value (as high as 3,400 mg per 100 ml) so that the load/Tm_G ratio, even though calculated on the basis of the control value for Tm_G, was maintained well in excess of unity in almost every study (Tables I and II). As another means of evaluating the mass of functioning tissue, Tm_D (control values in twelve dogs = 0.74 ± 0.26 mg per minute per kg body weight) was measured on ten occasions in 8 dogs at the same time as glucose Tm. With hypotension an effort was made to increase the plasma levels of Diodrast, but the changes obtained were much less than those for plasma glucose concentrations (from control values of 20 to 48 mg per 100 ml to as high as 82 mg per 100 ml after hemorrhage). Nevertheless, load/Tm_D ratios for Diodrast (computed on the basis of an assumed value for renal plasma flow as at least four times the filtration rate) were nearly always maintained in excess of 2.0 even though the control value for Tm_D was used in the computation. The likelihood of a simultaneously equivalent decrease in load for both tubular reabsorption and secretion, by roughly the same change in delivery (by GFR for Tm_G and renal blood flow for Tm_D), and in the plasma concentration would seem to be very small under the conditions of these experiments. The results obtained in ten successful studies are presented in Table I and Figure 3. The values of Tm_D and Tm_G in these experiments (Figure 3) were found to decrease together over a very wide range from 100% to less than 10% of the control values. Although there was obvious scatter about the line of equal change (the dashed line in the figure),

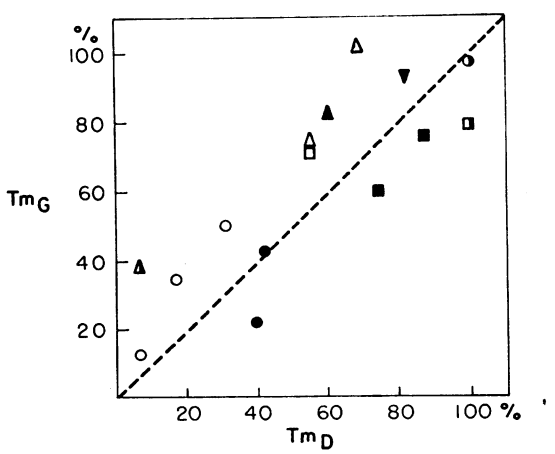

FIG. 3. CORRELATION OF TRANSPORT MAXIMUM FOR GLUCOSE (T_{MG}) AND DIODRAST (T_{MD}) AFTER HEMORRHAGE. The data fall about the dashed line of equal change in the two values. The symbols refer to individual experiments (Table I) as follows: ▼ Emily I, ◨ Florence, ● Gloria II, □ Irma, ■ Jackie, ◭ Leonia, ▲ Karla II, ◑ Ortrude I, ○ Ortrude II, △ Gloria III.

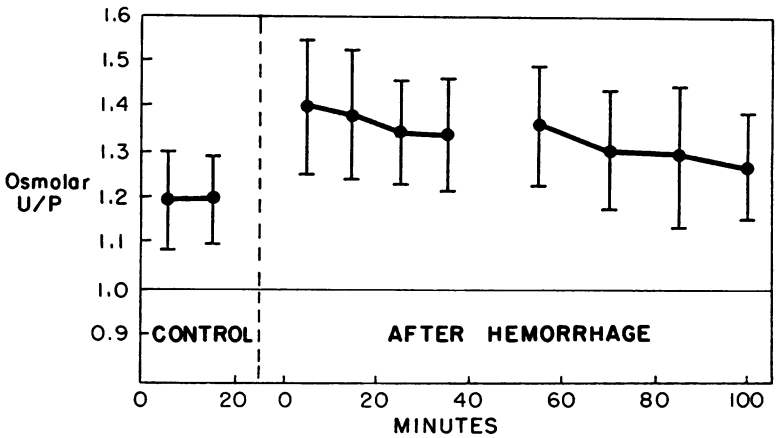

FIG. 4. CHANGE IN URINARY OSMOLARITY AFTER HEMORRHAGE. The osmolar urine/plasma (U/P) ratio is presented as the mean value ± the standard deviation for each collection period, two during the control before removal of blood, four during the 40 minutes after the initial hemorrhage, and four at longer intervals during the hour after a second hemorrhage, indicated by the break in the continuous line. The osmolar U/P ratio increased abruptly and then decreased slowly after bleeding. A second hemorrhage checked the descent of the curve and in many animals induced a slight rise in the U/P ratio but tended to fall progressively thereafter.

the correlation was highly significant ($r = 0.76$, $p < 0.001$). Moreover, in individual experiments in which values were obtained in more than one period after control, Tm_D and Tm_G closely paralleled the line of equal change in three of four animals.

These considerations appear to be consistent with the view that function of a fraction of nephrons ceased altogether during hypotension, presumably as filtration fell to, and below, some critical level, with a resultant equivalent reduction in both maximal reabsorption of glucose from filtrate and removal of Diodrast from perfusate. Further evidence that changes in the values for Tm could not be ascribed to unloading was noted in the high values for urinary output and concentration of glucose during the hypotensive period. Even with a fall in Tm_G to 22% of control in Gloria II, for example, the urinary glucose output amounted to almost 50% of the filtered load (Table II). This phenomenon was noted in each instance, indicating that more than sufficient glucose to saturate the transfer system had been presented to the tubules engaged in urine formation. However, tubular cellular dysfunction, rather than unloading, might be argued to have affected both secretory and reabsorptive activities to the same extent. If this were true, the urinary composition would be expected to resemble that of glomerular filtrate. To evaluate this possibility, urinary sodium, potassium, and osmolar excretion were studied under precisely the same conditions. Although Diodrast plasma levels were maintained in the standard manner, glucose Tm alone was measured, to keep the volume of blood samples taken for analytical purposes within roughly the same limits. During the hypotensive periods even the small quantities withdrawn for this purpose often critically interfered with maintenance of a steady state.

Electrolyte and water excretion. As we had expected, our control data (Table II and Figures 4 and 5) demonstrated the changes observed by others (14, 15) to be characteristic of an osmotic diuresis. The urine flow in the control periods was high, reaching an average value of 11.6 ± 5.2 ml per minute ranging from 6.9 to 22.8 ml per minute, and accounting for 13 to 41% of the GFR [$V(\text{urine flow})/C_{In} = 28.5 \pm 6.7\%$], as a consequence of the large output of glucose. Sodium excretion averaged 1,018 ± 363 μEq per minute, or 14.4 ± 5.0% of the filtered load (C_{Na}/C_{In}), which ranged from 5.7 to 23.1%. Potassium excretion was also markedly increased to

106 ± 40 μEq per minute, or 55.1 ± 25.3% of the filtered load (C_K/C_{In}) on the average, with a range 27 to 81%, except in one animal (Carmen II) where it reached a level of 152.4%. The large output of glucose, sodium, and potassium salts always resulted in an osmolal concentration of the urine in excess of that of the plasma, despite the excessive output of water. The control urinary/plasma osmolal concentration ratio (U/P_{osm}) averaged 1.195 ± 0.10 (Figure 4) and ranged from 1.05 to 1.43. The $T^c_{H_2O}$ ($T^c_{H_2O} = C_{osm} - V$), the amount of solute-free water abstracted from the urine, presumably in the collecting ducts, ranging from 0.98 to 4.61 ml per minute during the control periods, averaged 2.19 ± 0.96 ml per minute.

With hemorrhage the urine flow decreased sharply but remained within measurable limits in every animal. In all but one (Table II), V remained at levels in excess of 0.5 ml per minute even though arterial pressure fell to as low as 33 mm Hg, or to 30% of the control values. The urine flow decreased more than filtration so that the V/C_{In} ratio fell significantly to 18.3 ± 7.6% immediately after hemorrhage and showed little tendency to fall thereafter even with further bleeding (after first hemorrhage: 17.6 + 6.3; second: 19.0 ± 8.8). This phenomenon implies a relative augmentation in water reabsorption by the tubules, maintained in the face of increasing circulatory inadequacy and clearly opposed to the argument that the tubules had become relatively inert conduits of filtrate. Hence the fall in glucose Tm may be construed as evidence of a decrease in the active nephron population. Since the fall in GFR/Tm_G indicated a simultaneous reduction in the delivery of filtrate to tubular tissue, the slower passage of filtrate down the

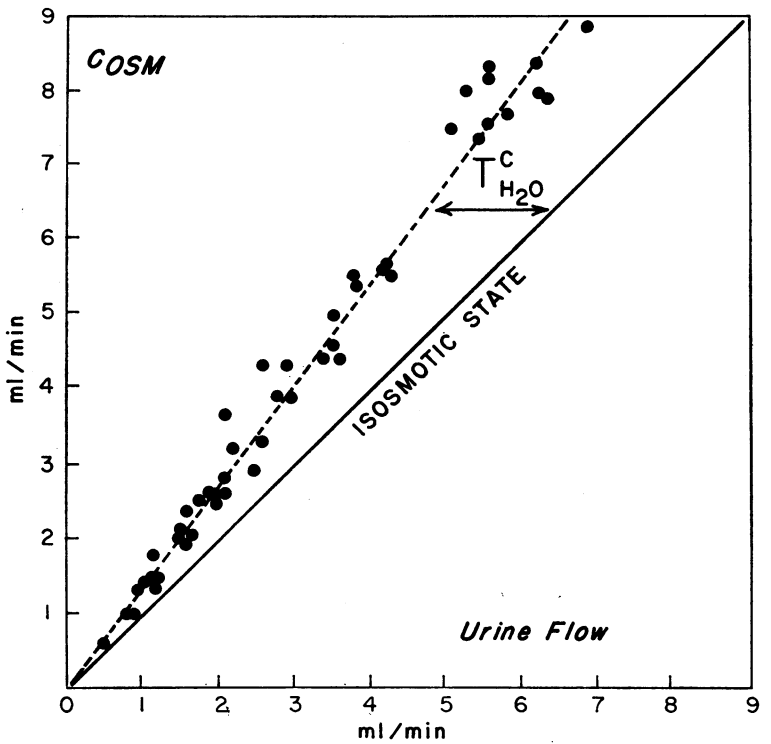

FIG. 5. RELATIONSHIP BETWEEN OSMOLAR CLEARANCE (C_{osm}) AND URINE FLOW AFTER HEMORRHAGE. Only the point for the values for C_{osm} and urine flow during the first posthemorrhage period for Natalie (Table II) fails to fall within the boundaries of this chart. All the data cluster closely about the dashed regression line ($y = -0.03 + 1.36x$, $r = 0.99$), indicating a relatively fixed osmolar U/P ratio after hemorrhage under the conditions of these studies. The $T^c_{H_2O}$ decreased regularly as urine flow fell after blood loss.

tubules may be inferred to have permitted a relative increase in the uptake of water.

This view also finds some support in the observation that sodium output diminished relative to filtration to an even greater extent with hypotension, the C_{Na}/C_{In} ratio (average for all figures = 1.76 ± 2.70%) falling in most instances to less than 1.0% and in some to 0.1% or even less (Table II). In three dogs (Xanthine I, Yolanda, and Amalia; Table II), the plasma sodium concentration fell also, but in the remainder this tendency was counteracted by the administration of sodium chloride solution (perhaps with too much success in Katrina, in whom control levels of 188 mEq per L were attained). The second hemorrhage nearly always resulted in a further fall in C_{Na}/C_{In}, though of much more modest dimensions (first hemorrhage = 2.44 ± 2.09%; second hemorrhage = 1.08 ± 3.10%). In three animals (Dalilah, Irene, and Katrina; Table II), however, a striking increase in C_{Na}/C_{In} occurred in the last periods of the study. "Failure" of renal tubular function resulting from prolonged hypoxia may possibly have been responsible. In these animals hemorrhagic hypotension proved to be irreversible, leading to death within 18 hours. There is no evidence that augmented output of glucose, a rise in plasma sodium concentration, or increased filtration could have been implicated. Indeed, both C_{In} and Tm_G decreased in all three without significant change in C_{In}/Tm_G ratio (Table II).

Perhaps the resultant lack of sodium for exchange with potassium in the distal tubule accounted for the reduction in potassium clearance during hemorrhagic hypotension (16). Certainly potassium excretion fell off (to an average of 32.7 ± 8.5 μEq per minute) to a greater extent than C_{In}, the C_K/C_{In} ratio always decreasing after the initial hemorrhage and decreasing in most instances still more after the second to as low as 12.4% (Table II) (total after hemorrhage = 28.9 ± 10.2%; after first hemorrhage, 32.7 ± 8.5; after second, 25.2 ± 10.6). In none was there evidence of excretion in excess of the filtered load after hemorrhage. The plasma potassium concentration decreased significantly in several animals but remained unchanged in the majority despite the maintenance of marked hyperglycemia. Potassium clearance also decreased more than Tm_G. Since potassium excretion appears to be referable, for the most part if not entirely, to tubular secretion, both the reduction in active tubular mass and a fall in active transfer from blood to urine must be called upon to explain these observations.

Despite the marked reduction in the output of sodium and potassium salts, the urinary osmolal concentration always increased during the hypotensive phase of each study (Figure 4). The osmolal U/P ratio increased immediately, rising to a mean value of 1.40 ± 0.15 and tending on the average to drift down thereafter. With the second hemorrhage the U/P ratio tended to rise slightly or to persist relatively unchanged for 20 to 30 minutes before again resuming the downward drift in association with a further reduction in urine flow. The osmolal U/P ratio returned to the control level in a small number of dogs in whom the studies were sufficiently protracted, even then approaching but never quite reaching a value of 1. All values for urine flow, after hemorrhage, were closely correlated with the osmolal clearance ($r = 0.99$) and clustered tightly about a regression line that passed through the origin and had a slope of 1.36 (Figure 5). The latter agreed with the average value for osmolal U/P ratio of 1.35 ± 0.13. The relatively constant relationship between C_{osm} and V throughout the hypotensive period and over a range of urine flows from 0.1 to 8 ml per minute appears to have arisen as a result of the osmotic load imposed by the large output of glucose. In the control peiods, glucose and the measured electrolytes (sodium and potassium with their corresponding anions) contributed almost equally to the total osmolal content of the urine and accounted for upwards of 94% of the total in most animals. With hemorrhage and the virtual disappearance of electrolytes from the urine, glucose constituted the bulk of the osmolal excretion, accounting, however, for only about 85% or less of the total. The deficit noted under these conditions presumably must have been made up by urea or some other undetermined solutes. The glucose clearance approached the GFR under the conditions of these experiments, and the values for C_{osm} and C_{In} were correlated after hemorrhage ($r = .438$), although C_{osm} tended to fall more than C_{In} (total after hemorrhage = 23.6 ± 7.9%; after first hemorrhage, 23.8 ± 7.3; after second, 23.3 ± 8.6).

The $T^c_{H_2O}$ always increased relative to filtration, in keeping with the fall in V/C_{In} ratio. Presumably the renal medullary concentrating mechanism remained effective throughout a period of at least 1½ hours of severe hemorrhagic hypotension, maintaining the continued abstraction of free water and an osmolal U/P ratio in excess of 1. The gradual fall in U/P_{osm} may be attributable to a critical reduction in the supply of sodium salt for transfer by the tubules to the medullary interstitial fluid and to the slow "washout" of the medulla-collecting duct concentration gradient in conformity with the hypothesis of the countercurrent mechanism (17).

Discussion

The findings of this study are consistent with the view that the nephrons of the canine kidney are not affected uniformly by the changes in perfusion and in perfusing pressures that are produced by graded hemorrhagic hypotension. In every animal the GFR fell with the arterial pressure and, for the group as a whole, fell more or less as a linear function of the arterial pressure. This could be construed as evidence that all glomeruli remained in operation and that the head of pressure in each was the same, falling with the arterial pressure without interference by local vasomotor responses once the fall had begun. All glomeruli appeared to contribute to urine formation, with the decrement in GFR down to approximately 50% of the control values, since the values of both glucose and Diodrast Tm were maintained unchanged to that level. At lower levels, however, this interpretation was invalidated by a fall in both glucose and Diodrast Tm. Although a reduction in Tm might have been attributable to the technical difficulty of maintaining an adequate load for transfer in excess of the saturation level, it is most improbable that both values would have been reduced simultaneously to the same extent by such a mechanism, particularly in view of the persistent and heavy glycosuria that pointed to continued saturation of the glucose transfer system. Cellular dysfunction as a result of hypoxia or other causes also seems, for several reasons, an unlikely explanation for the changes observed. First, the transfer maxima changed relative to the arterial pressure level rather than to duration of the pressure change in these studies; second, even severe hypoxia has been shown to have no effect per se upon these measurements (18); and third, the tubular capacity to reabsorb water and electrolytes remained intact. Since similar changes in transfer maxima were noted in dogs by Lauson and Thompson (PAH Tm) (16) and Thompson and Barrett (glucose Tm) (15) when renal arterial pressure was lowered by means of a balloon inflated in the aorta, the fall in hematocrit, produced by hemorrhage in many of these experiments, may be eliminated as an important causal agent. Our conclusion is therefore that hemorrhagic hypotension in the dog results in elimination of a fraction of nephrons from function, the percentage affected increasing progressively at lower and lower levels of blood pressure. The development of cortical ischemia and cortical necrosis when renal blood flow is markedly reduced, as in the work of Trueta and other workers (6, 19), apparently as a result of higher resistance to perfusion in this region, suggests that cortical nephrons probably comprise the majority of those eliminated.

Particularly noteworthy was the observation that urine could not be obtained when arterial pressure was approximately 30 mm Hg or less (Figure 1). This finding is strikingly at variance with those of many other workers (12, 17, 20) who have found that urine flow ceases during hemorrhagic hypotension in the dog when arterial pressure falls to about 60 mm Hg. At that pressure in our study the GFR was approximately 50% of the control value on the average and well above it in many animals. This discrepancy probably arises from the maintenance of an osmotic diuresis in contrast to the oliguria and hydropenia before hemorrhage in other investigations. Presumably, in the absence of an osmotic diuretic agent, all of the filtrate may undergo complete reabsorption within the tubules when GFR is reduced by 50% or more.

The high plasma glucose concentrations achieved in the course of these studies apparently assured the output of urine from every nephron in which filtration persisted, thus making possible detection of a correlation between arterial pressure and GFR with a pressure axis intercept close to the plasma oncotic pressure. For

the same reason, the use of mannitol might be expected to yield, at any given arterial pressure, higher values than inulin for GFR. Data bearing specifically upon this point have not been obtained. Urine flow's tendency to vary in proportion to mannitol clearance and independently of inulin clearance during shock in man (21) has been interpreted as an "osmotic accident" that produces a difference only in urine flow, not in filtration rate. The present data suggest, however, that the diuretic action of mannitol may serve to enhance the measured filtration rate.

Indeed, a number of recent reports (22–24) suggest that osmotic diuresis with mannitol may be effective in preventing or ameliorating renal dysfunction during traumatic and lengthy surgical procedures, indicating that maintenance of the outflow of urine is beneficial in some manner, perhaps by the "washout" of damaging substances. The complete reabsorption of filtrate within some tubules could conceivably lead to the local deposition of nonreabsorbable materials with accumulation to cytotoxic levels at some point and, ultimately, the production of localized tubulorrhexic lesions (6). Under these circumstances the maintenance of tubular flow could be protective by preventing the formation of accretions within the tubular lumens. The measurement of glucose Tm, necessarily involving the imposition of an osmotic diuresis, is impossible to use as a guide to the functional activity of the nephron population during the study of the hydropenic, oliguric state. The suggestion may be made that the cessation of urine flow in the hydropenic animal at 60 mm Hg implies a progressive reduction in the nephron population active in urine formation from the control to 0 at that point. In the absence of a means of estimating the active tubular mass, it is impossible at present to say whether GFR decreases less than, more than, or to the same extent as the nephrons producing urine throughout this range. Until this question is settled, ascertaining whether any change in urine formation associated with a decrement in GFR arises as a result of an alteration in tubular cellular function or in the pattern of the residual operative nephron population is difficult. This dilemma is given point in recent studies reported by Levinsky and Lalone (25) and by Stein, Bercovitch, and Levitt (26) that have yielded results indicating diminished tubular reabsorption of sodium in the dog relative to any given filtered load when filtration rate is reduced. Here, elimination from function of those nephrons predominantly active in sodium reabsorption could have left an active population dominated by units that normally excrete a larger fraction of the filtered sodium, thus producing a rise in sodium excretion relative to load, which could not be attributed to an intrinsic change in tubular transfer. Since Stein and his associates demonstrated this phenomenon unilaterally when renal arterial pressure was lowered in one kidney by compression, a humoral factor interfering with sodium reabsorption seems unlikely. Conceivably the tubular cells could have responded in this way to the fall in blood flow, intrarenal tension, or delivery of filtrate, but before this conclusion is warranted, further studies must be made to assess nephron participation.

Glomerular filtration decreased progressively and disproportionately as arterial pressure fell in the course of the present study so that the GFR/Tm_G ratio and the filtered load imposed upon each active nephron decreased. Presumably for this reason, even in the face of an osmotic diuresis, the fall in GFR was associated with a marked reduction in sodium and water output and with a rise in the osmolal concentration of the urine. The slower flow of filtration down the tubules may have resulted in prolonged contact between the filtrate and the absorbing cells, resulting in augmentation of sodium and water reabsorption. Similarly slower perfusion of the collecting ducts may have resulted in an immediate increase in osmolal U/P ratio as a closer agreement was achieved between the osmotic pressures of the urine in the collecting ducts and of the papillary interstitial fluid. If this was so, then the osmolal U/P ratio evident in the period immediately after the initial hemorrhage probably reflected the osmotic concentration maintained within the papilla by the countercurrent mechanism during the control periods. Maximal vasopressin stimulation and the enhanced supply of sodium salts made available distally by the increase in outflow from the proximal tubules with the glucose overload did not suffice to produce a urinary osmolal concentration much in excess of the plasma. Certainly the levels that develop with hydropenia and

relatively low rates of urine flow were not encountered. Selkurt (27) observed much more marked increments of U/P_{osm} in hydropenic, oliguric dogs after hemorrhage. We surmise that the difference in preliminary preparation of the dogs in the two studies may have resulted in a fundamental difference in papillary interstitial osmolal concentrations in the control periods, possibly dependent upon local circulatory factors. In any case, the osmotic U/P ratio tended to remain unchanged in our studies during a prolonged period of hypotension despite a marked reduction in filtration of sodium salts that could not be compensated by the increment possible in sodium reabsorption. The value did tend to drift toward the control levels with time, though a second hemorrhage retarded this change or even reversed it. In view of the data brought forward by Boylan and Asshauer (17) showing that the osmolal concentration of the canine papilla tends to fall gradually after hemorrhage, the fall observed in U/P_{osm} may reasonably be attributed to gradual washout of papillary sodium salts. The observed reduction in $T^c_{H_2O}$ can be explained by the same mechanism.

Acidosis is an inevitable side-effect of hemorrhage, largely because of the accumulation of lactic acid (28). The resultant formation of a highly acidic urine might well contribute to the changes in sodium and potassium output. The fall in potassium clearance relative to inulin clearance has been observed, however, during renal ischemia produced by renal arterial obstruction, presumably because the "distal secretion of K (i.e., exchange with Na) must decrease by reason of a lack of anions destined for excretion" (16). Acidosis, per se, would simply be expected to enhance this effect by providing an excess of hydrogen ions leading to suppression of potassium secretion (29). In fact, all the changes in maximal tubular activity and in the excretion of water and electrolytes observed in the studies reported in this paper are most readily interpreted as attributable chiefly to alterations in nephron population and balance. Relatively simple physical shifts such as those involved in defective glomerular-tubular and intertubular loading and in the "washout" of papillary osmolar activity appear to be involved, rather than metabolic change, either intrinsic or extrinsic to the kidney.

Summary

The maintenance of function within the nephron population was investigated in 32 normal, well-hydrated, anesthetized (with pentobarbital) dogs on 42 occasions during graduated hemorrhagic hypotension. Tubular activity was assessed in terms of maximal tubular glucose reabsorption (Tm_G) in 35 studies, maximal Diodrast secretion (Tm_D) in 17, and the urinary content and output of sodium, potassium, and osmotically active solutes in 22. Very high concentrations of glucose and Diodrast were maintained throughout all experiments to assure both adequate tubular loading and comparable experimental conditions.

Glomerular filtration rate (inulin clearance) was found to be significantly ($r = 0.81$) correlated with arterial pressure. Filtration fell without change in Tm_G to levels as low as 40 to 60% of control in association with decrements in arterial pressure to or even below 75 mm Hg. With further reductions in pressure, Tm_G also fell but not to the same extent, so that the GFR/Tm_G ratio decreased progressively. At the same time, the tubular reabsorption of sodium and water increased relative to filtration in association with an increased osmolal concentration of the urine. Potassium clearance decreased relative to the inulin clearance. The osmolal U/P ratio tended progressively to return toward control after hemorrhage but did not fall below unity during the period (up to 2 hours) of study.

Since Tm_G and Tm_D were found to decrease proportionately under the conditions of these studies (15 simultaneous measurements after blood loss in 10 experiments), the fall in Tm could be ascribed to cessation of function in a corresponding fraction of the nephron population. Within the residual active nephrons, the filtration apparently decreased in proportion to the change in pressure. It may be inferred that a gradient of filtration pressure exists within the kidney, presumably on the basis of vascular path length, so that the more peripheral units are more greatly affected by a given pressure decrement than those located centrally. This interpretation is consistent with the observation that the renal injury of prolonged circulatory collapse is predominantly cortical. That a substantial

fraction of nephrons continued to form urine at pressures of less than 60 mm Hg, the level at which complete anuria occurs in hydropenic animals, suggests that the glucose osmotic diuresis assured a continued urinary outflow. Indeed, it may imply complete reabsorption of water in these nephrons, perhaps ultimately with local intratubular accumulations of nonreabsorbable solutes of cytotoxic levels, when urine flow is not so maintained. The changes in electrolyte output could be accounted for by the fall in GFR with a resultant prolongation of the contact between filtrate and absorbing cells that *1*) enhanced tubular reabsorption of sodium and water, *2*) reduced the availability of sodium for exchange with potassium, *3*) permitted closer osmotic equilibration between collecting tubular urine and medullary interstitual fluid, and *4*) ultimately depleted the medulla of the sodium necessary for the maintenance of the countercurrent concentrating system. The data indicate the need for caution in the interpretation of any change in urine formation solely on the basis of tubular cellular activity without reference to the possibility of nonuniform behavior of the nephron population.

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ANNOUNCEMENT OF MEETINGS

The American Federation for Clinical Research will hold its Twenty-first Annual Meeting in Atlantic City, N. J., at the Casino Theater on the Steel Pier on Sunday, May 3, 1964, at 9:00 a.m. Joint sectional meetings with The American Society for Clinical Investigation will be held on Sunday afternoon at Chalfonte-Haddon Hall, and additional meetings sponsored by The American Federation for Clinical Research will be held on Sunday evening.

The American Society for Clinical Investigation, Inc., will hold its Fifty-sixth Annual Meeting in Atlantic City, N. J., on Monday, May 4, at 9:00 a.m., at the Casino Theater on the Steel Pier, and in simultaneous programs with The American Federation for Clinical Research on Sunday afternoon, May 3, in Chalfonte-Haddon Hall.

The Association of American Physicians will hold its Seventy-seventh Annual Meeting in Atlantic City, N. J., at the Casino Theater on the Steel Pier on Tuesday, May 5, at 9:30 a.m., and in the Vernon Room, Chalfonte-Haddon Hall, on Wednesday, May 6, at 9:30 a.m.