

The Postobstructive Kidney. Observations on Nephron Function after the Relief of 24 hr of Ureteral Ligation in the Dog

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ABSTRACT After the relief of 24 hr of complete unilateral ureteral obstruction in the dog, the experimental kidney is characterized by a decrease in filtration rate and an increase in fractional and often absolute excretion of sodium before and after the administration of mannitol. In the hydrated state, the failure to conserve sodium is associated with increases in fractional free water clearance and fractional sodium supply to water-freeing sites signifying that the augmented sodium excretion is derived from a proximal source. In the hydropenic state there is decreased fractional free water reabsorption, and sometimes free water excretion, in the postobstructive kidney. An early plateau in free water reabsorption is associated with an increased fractional excretion of sodium. These findings are attributed to the early development of distal nephron impermeability to water as a result of enhanced distal tubular supply and transport of sodium. There is a decrease in maximal tubular reabsorptive capacity (T_m) of glucose in the postobstructive kidney which is, however, less marked than the decrease in filtration rate. The fall in filtration rate is to some extent likely due to a dropping out of nephrons from the circulation while the remaining nephrons are hypoperfused. The magnitude of the sodium reabsorptive defect is markedly exaggerated as the concentration of nonreabsorbable solute (mannitol) in the glomerular perfusate is increased. It is concluded that the postobstructive increase in sodium excretion during mannitol ad-

ministration is in part due to a limit in the capacity to reabsorb sodium against a concentration gradient in the proximal tubule.

INTRODUCTION

Obstruction of the urinary tract has been shown to have a variety of effects on renal function in man and dog. Many of the described abnormalities have included observations of excessive electrolyte excretion and/or impaired concentrating capacity during or after the period of obstruction. The predominant locus of damage has been variously assigned to both the proximal (1, 2) and distal (3-7) nephron. Suki, Eknoyan, Rector, and Seldin (8) in a study of unilateral chronic hydronephrosis in hydrated dogs have concluded that the major disturbance in the obstructive nephropathy is increased GFR (glomerular filtration rate)¹ per nephron leading to decreased proximal tubular reabsorption of sodium and hyperperfusion of the distal nephron. They further suggested that back-diffusion of solute free water was impaired in the collecting duct and possibly in the descending limb of Henle's loop by anatomic disruption of medullary tissue thereby permitting excessive urinary dilution.

In most of the reported studies, the period of obstruction has varied from a week to several months resulting

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¹ Abbreviations used in this paper: CH_2O , free water clearance; C_{osm} , solute clearance; GFR, glomerular filtration rate; PAH, para-aminohippuric acid; PAS, periodic acid-Schiff; POK, postobstructive (experimental) kidney; T, reabsorbed glucose; T^*H_2O , free water reabsorption; UKV, urinary potassium excretion; UNa, urinary concentration of sodium; UNaV, urinary sodium excretion; Uosm, urinary solute concentration.

in large falls in GFR which makes a comparison of data with a normal control kidney somewhat uncertain. As well, various degrees of gross anatomic change in the experimental kidney have been noted making it difficult to distinguish to what degree the described abnormalities have been due to anatomic distortion of the kidney and to what extent purely functional changes prevail. In order to overcome these limitations, a relatively brief period of 24 hr of unilateral ureteral obstruction was selected—an interval in which there is neither gross nor microscopic change in the experimental kidney.

In the present experiments, patterns of electrolyte excretion and diluting or concentrating capacity were investigated in hydrated or hydropenic dogs before and during a progressive mannitol diuresis after the relief of obstruction.

Our findings indicate that after a single day of obstruction there is a defect in proximal tubular reabsorption of sodium resulting in enhanced fractional sodium supply to and transport by the distal nephron, that this defect is exaggerated when proximal sodium reabsorption is subjected to a gradient imposed by a mannitol load, and that the inability of the postobstructive kidney to conserve sodium is present despite decreased glomerular perfusion in surviving nephrons.

METHODS

17 experiments were carried out in female mongrel dogs weighing 15–25 kg and maintained on regular commercial diets. The effects of unilateral ureteral obstruction on renal function were studied during hydration and hydropenia. Dogs were lightly anesthetized with thiamylal sodium, and under aseptic conditions a suprapubic midline incision was made and the bladder exposed. Two silk ties were tightly placed around the right ureter near the ureterovesical junction causing complete ureteral obstruction and the abdomen was closed. Animals were then returned to their cages and were generally awake within 1 hr after surgery. In the hydropenic studies, animals were kept without food or water for 20 hr after ureteral ligation and were given 5 U of vasopressin tannate in oil intramuscularly 12 hr before the renal function studies were begun. In the hydrated studies, animals were allowed free access to water. 24 hr after right ureteral obstruction, hydropenic animals were anesthetized with sodium pentobarbital and hydrated animals with chloralose and urethane. Priming doses of creatinine or inulin (and in some studies, para-aminohippuric acid [PAH]) were administered and followed by a sustaining infusion of these substances at concentrations sufficient to produce stable plasma levels. In the hydropenic studies, aqueous vasopressin, 50 mU/kg per hr was added to the sustaining infusion. The midline suprapubic incision was then reopened, the left ureter catheterized with polyethylene tubing and one or two control timed urine specimens collected. The right ureter was then incised above the site of obstruction resulting in a gush of clear urine. A catheter was inserted high into the decompressed ureter to avoid dead space errors. Timed urine specimens were simultaneously collected from each kidney at 10- to 50-min intervals depending on urine flow rate. Hepa-

rinized arterial blood specimens were obtained at the midpoint of each collection period.

In the hydropenic series, after one or two baseline periods, 10% mannitol in 0.2% NaCl or 10% glucose in 0.2% NaCl was infused into a foreleg vein at progressively increasing rates. In the hydrated studies, animals received 1–2 liters of either 2.0 or 2.5% glucose in 0.2% NaCl. After hydration, 2.0% or 2.5% mannitol in 0.2% NaCl was progressively infused. The experiments were carried out until urine flow rate failed to increase with further increases in the rate of infusion.

In six hydropenic studies, 7.5–12.5% glucose in 0.2% NaCl, rather than mannitol, was used as the loading solute so that glucose T_m (maximal tubular excretory capacity) could be determined in each kidney. In three studies T_m determinations were made after slowly increasing plasma glucose levels so that it could be noted whether or not initial glycosuria occurred simultaneously in both kidneys. In these studies, a minimum of 20 min was allowed for equilibration of the plasma glucose level after each increase in the rate of glucose infusion. In three other studies, plasma glucose was raised relatively quickly in the early periods, and glucose determinations were made only after plasma glucose levels had exceeded 400 mg per 100 ml.

Urine and plasma specimens were analyzed in all studies for Na, K, Cl, and osmolality. In the studies of glucose T_m, glucose was determined in plasma and urine using Glucostat Reagent.² Urine dilutions generally ranged from 500 to 1000. In some experiments, inulin and PAH were determined and in others, including all glucose T_m studies, creatinine was determined. Other determinations were performed using methods previously described from this laboratory (9).

The clearance of creatinine or inulin was used to represent effective GFR; the clearance of PAH was used to represent effective renal plasma flow. Filtered sodium load was estimated as GFR times plasma sodium concentration. No correction was made for the Donnan effect. Fractional sodium excretion was calculated as urinary sodium excretion (UNaV)/GFR times PNa. Solute clearance (Cosm), free water reabsorption (T^{*}H₂O), and free water clearance (CH₂O) were calculated in the usual way. Reabsorbed glucose (T) was calculated as GFR (cc/min) times plasma glucose concentration (mg/cc) — Uglucose V where Uglucose represents glucose concentration in urine (mg/ml) and V represents urine flow rate (ml/min). T_m glucose was taken as the mean of a variable number of determinations of T after this parameter had reached maximal values in that kidney and was relatively stable.

In two animals, renal biopsies from both kidneys were taken from 24 to 48 hr after unilateral ureteral ligation. Part of the biopsy material was fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin and periodic acid-Schiff (PAS) stain for light microscopy. The remainder was fixed in buffered 2% osmium tetroxide and embedded in Epon in preparation for electron microscopy.

RESULTS

Pathology. Longitudinal section of the control and experimental kidneys did not reveal any gross differences in the renal papillae or pelvi-calyceal systems.

Light microscopic sections in one of the postobstructive kidneys were entirely normal. In the second ex-

² Worthington Biochemical Corp., Freehold, N. J.

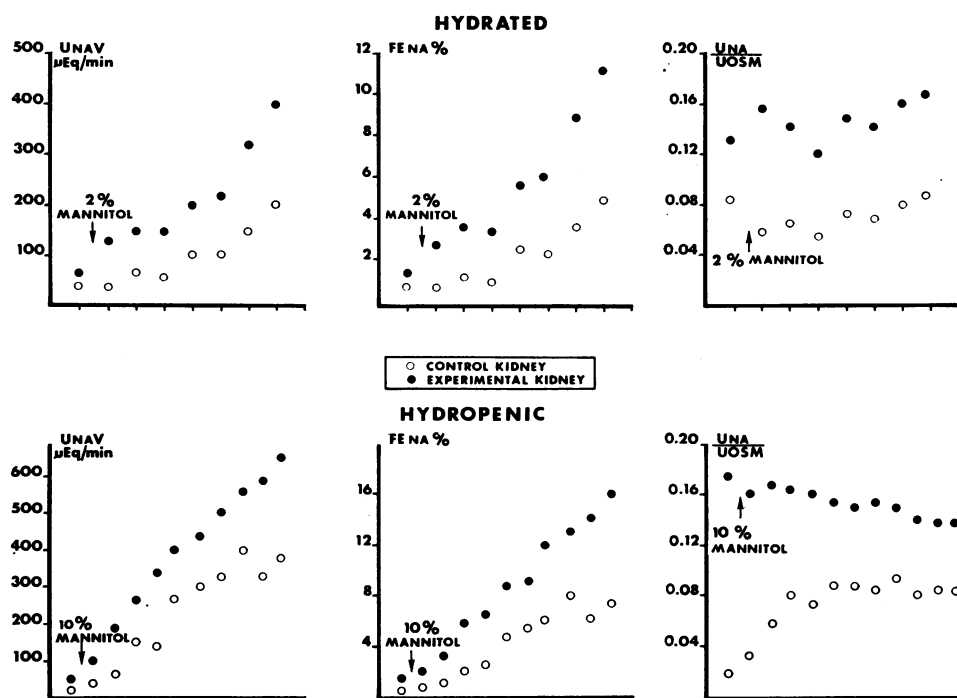


FIGURE 1 UNaV, FE_{Na} and UNa/Uosm in postobstructive and contralateral control kidneys during course of a typical hydrated and hydropenic experiment.

TABLE I
Hydrated Experiments. Comparison of Postobstructive Kidney and Contralateral Control with Regard to Electrolyte Excretion Diluting Capacity and Sodium Supply to the Distal Nephron

Experi- ments		GFR		UNaV		FE_{Na}		U_{KV}		CH_2O		$CH_2O/GFR \times 100$		$CH_2O + CNa/GFR \times 100$	
		CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP
		ml/min		$\mu Eq/min$		%		$\mu Eq/min$		ml/min		%		%	
1	A	47.9	26.3	7	121	0.1	3.5	11	8	4.27	1.73	8.9	6.6	5.9	10.1
	B	39.2	24.6	340	518	8.0	19.5	38	8	7.00	4.63	17.9	18.6	25.9	38.1
2	A	57.6	39.6	24	102	0.3	1.9	24	14	4.39	4.41	7.6	11.1	7.9	13.0
	B	47.7	33.1	242	386	4.3	9.9	30	28	7.90	6.32	16.6	19.1	20.9	29.0
3	A	26.9	12.9	46	73	1.4	4.6	23	10	2.06	0.74	7.7	5.74	9.1	10.3
	B	28.0	13.3	261	177	8.8	12.6	29	14	5.36	2.98	19.1	22.4	27.9	35.0
4	A	23.8	18.9	10	144	0.3	5.9	22	21	-0.81	1.04	-3.3	5.5	-3.1	9.0
	B	31.3	23.2	28	204	1.0	7.0	19	23	3.84	3.78	12.3	16.3	13.3	23.3
5	A	43.8	38.2	44	73	0.8	1.5	13	19	3.29	3.28	7.5	8.59	8.3	10.1
	B	37.0	33.9	186	405	4.2	10.8	37	52	5.42	4.95	13.7	14.6	18.2	25.4
6	A	30.7	25.7	22	114	0.6	3.8	31	158	2.30	2.00	7.5	7.7	0.8	11.5
	B	31.5	23.9	68	202	1.8	7.1	24	151	3.90	3.40	12.5	14.2	14.4	21.3
Mean	A	38.5	26.9	25	104	0.6	3.5	21	38	2.58	2.20	6.0	7.5	4.8	10.7
	B	35.8	25.3	189	315	4.7	11.1	29	46	5.57	4.34	15.3	17.5	20.1	28.7
P value	A	<0.02		<0.01		<0.01		NS		NS		NS		<0.05	
	B	<0.01		<0.05		<0.01		NS		NS		<0.01		<0.01	

GFR, glomerular filtration rate (Creatinine or Cinulin); UNaV, urinary sodium excretion; FE_{Na} , fraction of filtered load of sodium excreted; U_{KV} urinary potassium excretion; CH_2O , free water clearance; $CH_2O/GFR \times 100$, free water clearance as per cent of GFR; $CH_2O + CNa/GFR \times 100$, sum of free water clearance and sodium clearance as fraction of GFR, A, value before hypotonic mannitol infusion; B, value during hypotonic mannitol infusion. CON, control kidney; EXP, experimental (postobstructive) kidney.

TABLE II
*Hydropenic Experiments. Comparison of Postobstructive Kidney and Contralateral Control with
Regard to Electrolyte Excretion and Concentrating Capacity*

Experiments		GFR		UNaV		FEN _a		U _K V		T ^c H ₂ O max	
		CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP
		<i>ml/min</i>		<i>μEq/min</i>		<i>%</i>		<i>μEq/min</i>		<i>ml/min</i>	
6	A	25.2	19.6	2	6	0.1	0.2	28	20	1.17 (9)*	0.63 (8)
	B	24.6	20.5	397	569	15.3	28.8	98	102		
7	A	61.6	42.3	13	28	0.2	0.5	47	50	4.15 (13)	2.80 (12)
	B	48.5	39.4	317	614	5.2	12.5	70	134		
8	A	47.2	29.4	8	43	0.1	1.0	33	19	3.70 (8)	1.55 (6)
	B	39.3	35.2	388	704	7.7	15.6	71	84		
9	A	46.4	35.2	27	30	0.4	0.6	39	16	2.54 (9)	1.18 (8)
	B	39.4	33.8	322	362	6.2	8.2	165	116		
10	A	51.4	37.8	23	42	0.3	0.8	35	42	3.60 (14)	2.40 (14)
	B	51.0	47.3	234	567	3.6	7.8	83	133		
11	A	38.7	13.5	53	29	1.0	1.5	20	8	1.49 (9)	0.04 (5)
	B	39.9	27.6	414	448	9.8	15.3	50	31		
12	A	38.4	15.1	35	48	0.7	2.3	16	14	2.71 (12)	0.15 (8)
	B	45.7	24.9	465	535	9.0	19.0	70	77		
13	A	55.7	9.1	82	55	1.0	4.2	38	6	3.87 (10)	0.14 (7)
	B	37.9	28.9	343	1106	7.3	30.9	61	113		
14	A	67.6	24.6	22	15	0.2	0.4	64	16	2.60 (10)	1.37 (10)
	B	61.0	43.6	14	102	0.2	1.8	27	24		
15	A	62.1	14.6	104	31	1.2	1.5	50	13	3.30 (9)	0.35 (9)
	B	45.8	29.0	360	526	7.6	17.6	87	91		
16	A	57.7	17.6	13	15	0.2	0.6	24	9	4.30 (13)	1.32 (10)
	B	53.8	41.1	187	672	2.7	12.9	58	127		
Mean	A	45.6	23.5	35	31	0.5	1.2	36	19	3.03	1.08
	B	44.3	33.8	313	564	6.8	15.5	77	94		
<i>P</i> value	A	<0.001		<0.001		<0.05		<0.01		<0.001	
	B	<0.001		<0.05		<0.001		NS			

T^cH₂O max = maximum solute free water reabsorption; A = value before hypertonic mannitol or glucose infusion; B = value during hypertonic mannitol or glucose infusion; for other abbreviations see Table I.

* Numbers in parentheses represent the collection period in which the value was obtained.

perimental kidney there was a mild dilatation of the collecting tubules particularly in the outer zone of the medulla. A number of tubules in the medulla, particularly loops of Henle, contained hyaline casts. Several similar casts were also present in the control kidney.

Electron microscopy of tubular cells revealed non-specific changes of vacuoles and lipid droplets in both kidneys without any apparent distinction between the control and experimental kidneys.

Glomerular filtration rate (GFR). The mean GFR for the postobstructive (experimental) kidney (POK) and contralateral control was determined for each kidney.

The GFR in the postobstructive kidney was decreased in all studies, reductions ranging from 13 to 65% of the control kidney. In most studies the GFR tended to remain stable throughout the experiment; in others there were early progressive increments in GFR in the post-obstructive kidney which stabilized after five to six collection periods. Changes in renal plasma flow (RPF) paralleled those of GFR.

Sodium excretion. Despite the variable reduction in GFR, there was generally an increase in absolute sodium excretion in the experimental kidney before infusion of nonreabsorbable solute (Fig. 1, Tables I-IV). During

TABLE III
Representative

Period	Time	V		CCREAT		UN _A V		UN _A V/FN _V ×100	
		CON	EXP	CON	EXP	CON	EXP	CON	E
	<i>min</i>	<i>ml/min</i>		<i>ml/min</i>		<i>μEq/min</i>		<i>%</i>	
	0	Primes administered; constant infusion started: creatinine 20 mg/min,							
	20	2.5% D/W in 0.2% N _A CL I-V at 10 ml/min							
	70	Right ureter catheterized							
1	130-140	6.60	6.45	57.6	39.6	24	102	0.3	1.9
		2.5% mannitol in 0.2% N _A CL administered I-V at gradually increasing							
2	149-159	9.27	8.00	60.6	40.7	50	134	0.6	2.5
3	179-189	10.2	9.55	55.9	40.5	101	221	1.4	4.1
4	223-243	12.2	10.2	45.3	32.5	116	198	2.0	4.9
5	253-263	13.8	11.1	42.0	30.0	88	192	1.7	5.1
6	273-283	15.9	13.0	43.6	32.4	130	280	2.5	7.0
7	283-293	16.9	14.5	47.9	33.4	184	323	3.1	7.9
8	303-313	18.6	15.7	47.7	33.1	242	386	4.3	9.9

V, urine flow rate, CCREAT, creatinine clearance (GRF), C_{OSM} , solute clearance. For other abbreviations see Tables I and II.

mannitol or glucose diuresis, UNaV increased progressively in both kidneys and remained greater in the experimental kidney (mean hydropenic, 1.8 times control; mean hydrated, 1.7 times control) even at high rates of solute excretion (Fig. 1, Tables I-IV).

There was a consistent increase in the fraction of the filtered load of sodium excreted by the experimental kidney before the infusion of nonreabsorbable solute (mean hydrated, 6 times control; mean hydropenic, 2.4 times control) (Figs. 1 and 4; Tables I-IV, VI). As the diuresis progressed fractional sodium excretion in the experimental kidney rose at a more rapid rate than the control and showed a decreased tendency to level off at high fractional excretions (Figs. 1 and 4) mean hydrated 2.4 times control; mean hydropenic, 2.3 times control).

In addition, urinary concentration of sodium, UNa, was higher in the experimental kidney. Moreover, the fraction UNa/Uosm^a remained higher in the experimental kidney during simultaneous collection periods (Fig. 1, Tables III and IV).

Potassium excretion. In the hydrated studies, mean potassium excretion was higher in the experimental kidney before and during mannitol as well as during mannitol in the hydropenic studies (Tables I and II). Although mean K excretion was lower before mannitol in the hydropenic studies (Table II) this may be related to the fact that absolute sodium excretion was also lower,

since decreases in GFR were maximal at this time. Nevertheless in several individual experiments, both hydrated and hydropenic, K excretion was lower in the POK than in the control kidney although these were generally instances in which the POK showed only a small increase in absolute sodium excretion when compared to the control kidney.⁴

Diluting capacity. During hypotonic mannitol loading, CH_2O increased progressively in both kidneys, but was lower on the experimental side in which GFR was decreased (Fig. 2, Tables I and III). However, CH_2O may be adjusted for differences in filtration rate by the expression CH_2O/GFR times 100. This parameter, denoting the fraction of GFR which is excreted as solute free water, was higher in the experimental kidney in all studies after mannitol (Fig. 2, Tables I and III). Where the reduction in solute clearance⁵ was not excessive, this

⁴In some instances K excretion may be limited because the lower GFR in the POK may be due to some extent to nonfunctioning nephrons, as will be inferred later in the glucose Tm studies. In this situation it is apparent that at a time when UNaV is similar in both kidneys the K secretory sites of the functioning nephrons in the POK are subjected to a greater sodium supply per nephron than the control kidney. Since increments in UNaV may be associated with less than proportional increases in UKV, the POK would thereby be expected to have a somewhat lower UKV at similar levels of UNaV.

⁵Despite the consistent reduction in GFR and filtered solute load in the experimental kidney, levels of solute excretion were generally similar during simultaneous collection periods. Differences in back diffusion of solute free water as a result of differences in solute excretion (11) are thereby minimized.

^aIn order to correct for changes in sodium concentration consequent upon alterations in water reabsorption alone, UNa was factored by total urinary solute concentration, Uosm. Since plasma sodium is identical in both kidneys, increases in UNa/Uosm represent decreases in net transtubular-sodium concentration gradient (10).

Hydrated Experiment

UN _A /U _{osm} ×100		C _{osm}		CH ₂ O		CH ₂ O/GFR ×100		CH ₂ O + CNA/ GFR × 100	
CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP
%		ml/min		ml/min		%		%	
PAH 4 mg/min. Left ureter catheterized.									
3.56	16.6	2.21	2.04	4.39	4.41	7.62	11.1	7.9	13.0
rates									
6.0	17.9	2.80	2.52	6.47	5.48	10.7	13.5	11.3	16.0
7.92	17.8	4.22	4.11	5.98	5.44	10.7	13.4	12.1	17.5
6.33	12.4	6.22	5.45	5.98	4.75	13.2	14.6	15.2	19.5
4.24	10.7	7.09	6.08	6.71	5.02	16.0	16.7	17.7	20.0
6.68	12.7	8.64	7.32	7.26	5.68	16.7	17.5	19.2	24.5
6.65	13.0	9.30	8.32	7.60	6.18	15.9	18.5	19.0	26.4
7.55	13.8	10.7	9.38	7.9	6.32	16.6	19.1	20.9	29.0

parameter was also higher in the experimental kidney before mannitol (Tables I and III).

To determine whether there was any consistent alteration in the fraction of the filtered sodium load reaching distal water-freeing sites, an index of fractional distal sodium supply, CH₂O + CN_A/GFR times 100 was utilized (10). In all studies, this index was consistently

higher in the experimental kidney (Fig. 2, Tables I and III).

Concentrating capacity. During the infusion of mannitol T^hH₂O generally increased bilaterally. The rate of increase in T^hH₂O was somewhat lower in the experimental kidney and the maximal level of T^hH₂O was attained earlier in time and at a greater fractional so-

TABLE IV
Representative Hydropenic Experiment

Period	Time	V		GFR		UN _A V		UN _A V/FN _A ×100		UN _A /U _{osm} ×100		C _{osm}		T°H ₂ O	
		CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP
	<i>min</i>	<i>ml/min</i>		<i>ml/min</i>		<i>μEq/min</i>		<i>%</i>		<i>%</i>		<i>ml/min</i>		<i>ml/min</i>	
	0	Primes administered; constant infusion started: Creatinine 17 mg/min, PAH 3.3 mg/min and Aqueous Pitressin 50 mμ/kg/hr in 0.9% N _A CL Delivered at 0.34 ml/min. Left ureter catheterized													
	115	Right ureter catheterized													
1	152–185	0.22	0.28	49.3	28.2	12	26	0.2	0.8	3	16	1.37	0.71	1.15	0.43
2	185–222	0.20	0.30	47.2	29.4	8	43	0.1	1.0	2	18	1.26	0.77	1.06	0.47
	234	10% Mannitol in 0.2% N _A CL administered I–V gradually increasing rates													
3	235–245	0.73	1.09	53.8	34.9	18	106	0.2	2.0	2	17	2.42	2.05	1.69	0.96
4	256–266	1.50	2.28	48.3	36.9	60	186	0.9	3.5	5	17	3.65	3.56	2.15	1.28
5	276–286	2.60	3.68	44.6	30.5	129	261	2.0	6.0	8	17	5.37	5.05	2.77	1.37
6	286–296	3.97	5.30	51.3	39.3	168	355	2.4	6.6	7	16	7.45	6.85	3.48	1.55
7	316–326	5.80	6.65	41.2	30.2	261	401	4.7	9.8	8	15	9.49	8.02	3.69	1.37
8	336–346	7.30	8.10	43.0	33.4	307	446	5.3	9.9	8	14	11.00	9.56	3.70	1.46
9	356–366	8.20	8.99	43.5	31.7	336	515	5.9	12.3	8	15	11.9	10.38	3.70	1.39
10	366–376	8.90	10.0	38.2	32.3	390	560	8.0	13.5	9	14	12.6	11.4	3.7	1.4
11	387–397	9.60	11.3	38.4	33.0	317	597	6.4	14.1	7	14	13.0	12.7	3.4	1.4
12	397–407	10.6	12.4	39.0	32.1	376	657	7.5	16.0	8	13	13.8	13.8	3.2	1.4
13	407–417	11.4	13.6	39.3	35.2	388	704	7.7	15.6	7	13	14.4	14.8	3.0	1.2

For abbreviations see Tables I-III.

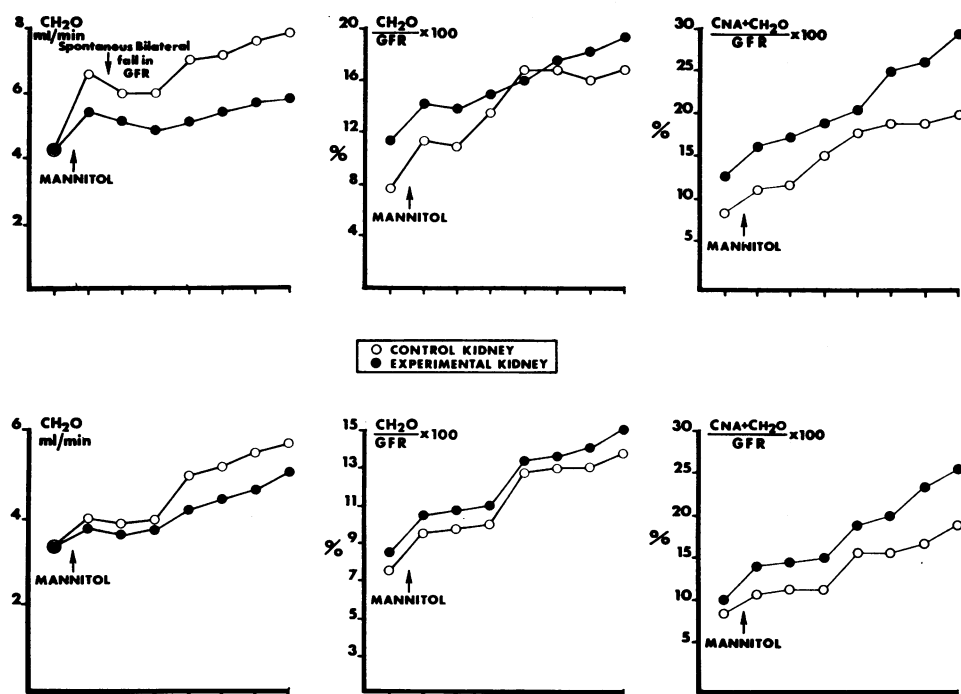


FIGURE 2 CH_2O , $\text{CH}_2\text{O}/\text{GFR}$, and $\text{CNa} + \text{CH}_2\text{O}/\text{GFR}$ in postobstructive kidney and contralateral control in two hydrated experiments.

dium excretion when compared with the control kidney (Fig. 3, Tables II, IV, and VI). There was a stable plateau in both kidneys followed by a gradual decrease in $\text{T}^{\circ}\text{H}_2\text{O}$ at high rates of solute excretion (Fig. 3, Table IV).

To adjust for decreases in GFR in the experimental kidney $\text{T}^{\circ}\text{H}_2\text{O}/\text{GFR}$ was calculated in consecutive collection periods for each kidney. The quantitative relationship between the two curves remained similar to the original $\text{T}^{\circ}\text{H}_2\text{O}$ curves from which they were derived (Fig. 3).

In several studies, the greatest reduction in GFR occurred in the early periods after the release of obstruction. The GFR in the experimental kidney gradually increased and then stabilized, generally at a value greater than 50% of the control. In these experiments, absolute sodium excretion was sometimes lower in the experimental kidney, but fractional sodium excretion remained higher throughout each study (Fig. 4, Table II, experiments 11, 13, 15). Early in these studies, unusually low levels of $\text{T}^{\circ}\text{H}_2\text{O}$ (less than $\frac{1}{2}$ ml) were reached in the experimental kidney and there was a rapid fall in urinary osmolality to levels below the level of plasma resulting in the formation of negative $\text{T}^{\circ}\text{H}_2\text{O}$ or CH_2O (Fig. 4). As fractional sodium excretion increased, CH_2O also progressively increased reaching levels of 2–3 ml per min (Fig. 4). The characteristics

of the $\text{T}^{\circ}\text{H}_2\text{O}$ curve of the control kidney were similar to those in experiments with modest GFR reduction.

Glucose T_m . In six of the hydropenic studies, the T_m glucose for each kidney was determined. This parameter was reduced in the experimental kidney in each study, but to a lesser degree than the reduction in GFR; a mean reduction in T_m of 35% compared with a mean reduction in GFR of 49%. It was found, therefore, that GFR/T_m glucose was consistently lower in the experimental than in the control kidney (Table V).

In three glucose-titration studies, plasma glucose was slowly raised to determine the level at which glycosuria first occurred. In two experiments initial glycosuria was noted in the control kidney at a lower plasma glucose level than in the experimental kidney; in the third glycosuria was detected simultaneously. A representative glucose titration experiment is presented in Table VI. The plasma glucose level was gradually raised from 90 to 732 mg per 100 ml. At a plasma glucose level of 221 mg per 100 ml glycosuria was present on the control side, but not on the experimental side. During the course of the experiment, $\text{T}^{\circ}\text{H}_2\text{O}$ is greatly decreased in the experimental kidney while fractional sodium excretion is higher.

In three studies in which a glucose load was administered in order to reach T_m levels without titration, blood glucose levels of at least 400 mg per 100 ml were

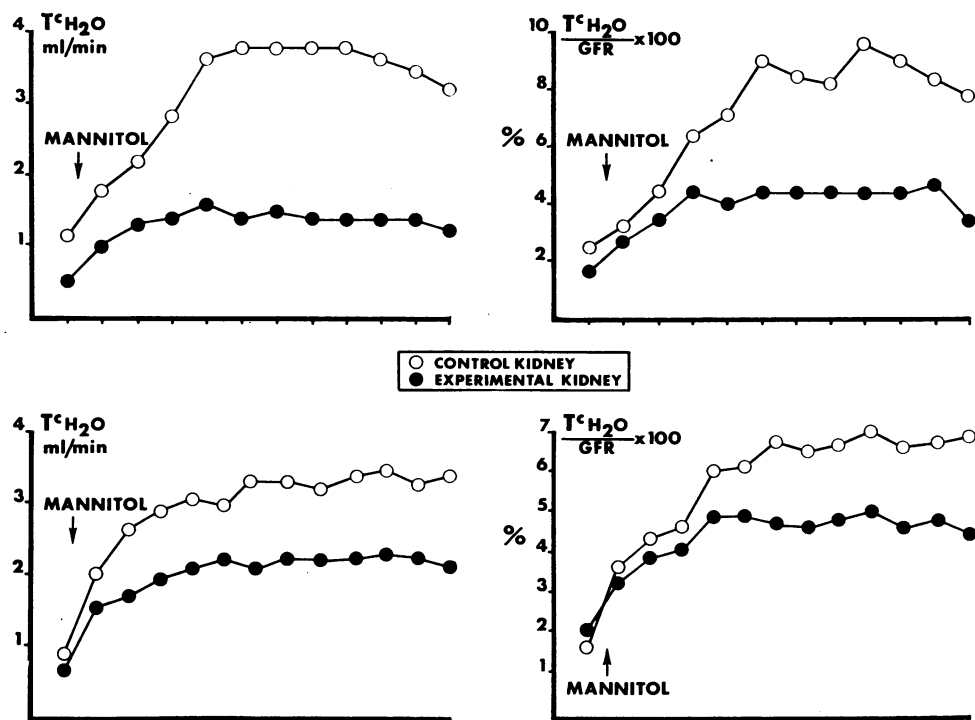


FIGURE 3 T^cH_2O and T^cH_2O/GFR times 100 in postobstructive kidney and contralateral control in two hydropenic experiments.

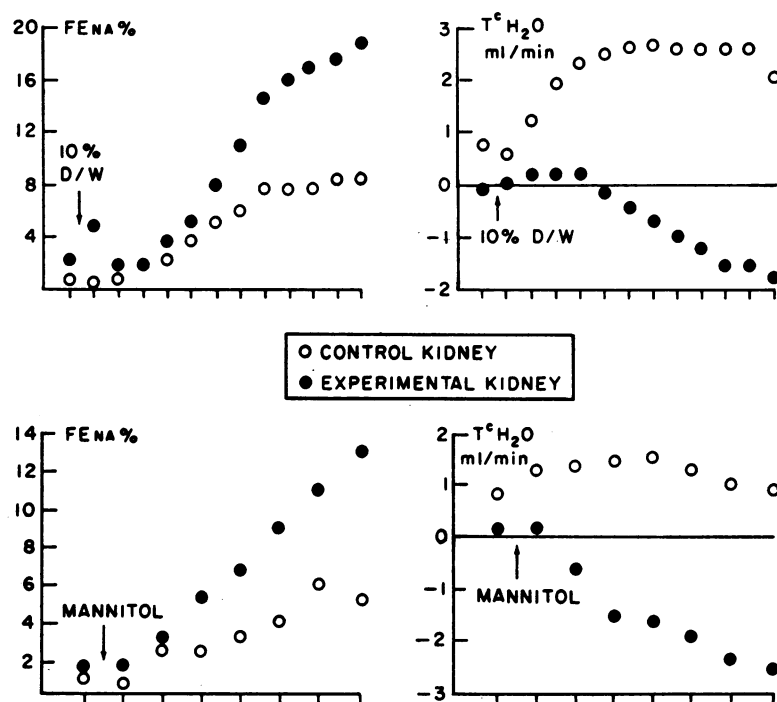


FIGURE 4 FE_{Na} and T^cH_2O falling to CH_2O in postobstructive kidney and contralateral control in two hydropenic experiments.

TABLE V
Glomerular Filtration Rate, T_M Glucose, and GFR/T_M Glucose
in Postobstructive Kidney and Contralateral Control

Experi- ment	Weight	GFR		T_M Glucose		GFR/T_M Glucose	
		CON	EXP	CON	EXP	CON	EXP
	kg	ml/min		mg/min			
11	19	40.8	24.5	105	94	0.39	0.26
12	23	50.6	20.8	153	81	0.33	0.26
13	20	59.8	22.9	198	100	0.30	0.23
14	22	63.1	41.8	180	127	0.35	0.33
15	22	71.0	32.6	173	103	0.41	0.32
16	19	63.7	35.5	170	115	0.38	0.31
Mean		58.2	29.7	163	103.3	0.36	0.28
P		0.001		0.01		0.01	

CON, control kidney; EXP, experimental kidney; T_M glucose, maximal reabsorptive rate of glucose.

noted early in the experiment at a time when there was marked depression of the GFR. However, by the time T_M glucose levels were reached GFR was stable.

DISCUSSION

In all studies, the postobstructive kidney showed a diminished capacity to conserve sodium with failure to establish a transtubular sodium concentration gradient comparable with that noted in the control kidney. This was reflected in a consistent increase in the fraction of the filtered sodium load excreted by the experimental kidney, frequent absolute increases in sodium despite the fall in GFR, and increased UNa/U_{osm} (Fig. 1, Tables I-IV and VI).

Some insight into the predominant tubular locus of decreased sodium reabsorption may be gained by the use of CH_2O and T^H_2O formation. Previous reports from this and other laboratories have utilized these param-

eters, in hydrated and hydropenic states, respectively, to evaluate the effects of diverse stimuli on sodium reabsorption at separate nephron sites. It is now generally accepted that in the hydrated state water is freed by the absorption of sodium from a water impermeable tubular segment primarily at, and probably also distal to, the ascending limb of Henle's loop. An agent which inhibits proximal sodium reabsorption would then increase distal sodium supply and CH_2O would rise, in large part because of the increase in sodium reabsorption at and beyond the ascending limb.⁸ Inhibition at the loop of Henle or more distal sites would either decrease CH_2O (13, 14) or leave it unchanged (15). In these terms CH_2O formation may be used as an indirect index of ascending limb sodium transport (15), and the sum of CH_2O plus CNa a rough estimate of distal sodium supply (10).

The uniform increases in $CH_2O + CNa/GFR$ in the POK suggests that there is enhanced fractional sodium supply to the distal nephron. Although CH_2O/GFR was not consistently elevated before mannitol when GFR tended to be lowest, this parameter was also increased in the POK during mannitol administration when GFR was stable. This further suggests that the enhanced fractional sodium supply resulted in increased sodium transport in the distal, water impermeable nephron. It therefore appears that while the proximal nephron reabsorbs less sodium after obstruction, the distal nephron largely retains its capacity for sodium transport.

⁸ It has been argued that the increase in free water might also result from a diminished rate of back-diffusion of collecting duct water as urine flow rate increases and the Na concentration in late distal tubular fluid rises (11). Nevertheless it is assumed that at high flow rates back-diffusion in the hydrated state is probably meager and this factor is currently assigned minor importance in the total rise in free water produced by increasing the distal supply of absorbable solute (12).

TABLE VI
Representative Glucose Titration Experiment

Period	Time	Plasma glucose	GFR		Glucose excretion		T glucose		T/ T_M glucose		Load/ T_M glucose		UNa/V $FN_A \times 100$		T^H_2O	
			CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP	CON	EXP
	min	gm%	ml/min		mg/min		mg/min				mg/min		%		ml/min	
	0	Primes administered. Constant infusion started: Creatinine 15 mg/min and aqueous Pitressin 50 mμ/kg per hr in 0.9% $NaCl$ delivered at 0.34 ml/min. Left ureter catheterized														
	60	Right ureter catheterized														
1	119-135	90	62.1	14.6	0	0	56	13.1	0.32	0.13	0.32	0.13	1.2	1.5	0.93	-0.03
	137	7.5% D/W I-V started														
2	170-200	122	64.0	17.1	0	0	78	20.9	0.45	0.20	0.45	0.20	0.7	1.0	1.00	0.09
3	234-268	180	69.4	20.6	0	0	125	37.1	0.72	0.36	0.72	0.36	1.0	1.1	1.18	0.15
4	268-312	221	72.5	27.6	7.3	0	153	61.0	0.88	0.59	0.93	0.59	1.3	1.2	1.48	0.20
5	327-351	306	72.2	33.8	55.0	2.8	166	100.0	0.96	0.97	1.28	1.00	2.1	1.6	2.00	0.27
6	351-399	360	75.1	32.2	96.0	11.0	174	105.0	1.01	1.02	1.56	1.13	1.7	2.0	2.38	0.31
7	404	12.5% D/W I-V started														
7	420-438	588	69.7	33.4	240.0	88.0	170	108.0	0.98	1.05	2.38	1.82	2.3	4.6	3.11	0.23
8	460-470	732	63.3	31.0	326.0	129.0	177	98.0	1.02	0.95	2.90	2.20	2.5	4.9	3.08	0.19

The results of the hydropenic studies are consistent with this conclusion. Although $T^{\circ}H_2O$ has also been used as an index of ascending limb sodium supply and transport (16), the demonstration by direct (17) and indirect (11, 18–20) means that hypotonic distal tubular fluid fails to reattain isotonicity may spuriously lower the $T^{\circ}H_2O$ value. Therefore as a solute diuresis increases distal sodium reabsorption, and frees more water, the calculated $T^{\circ}H_2O$ value may plateau or fall despite increases in ascending limb sodium transport and collecting duct water reabsorption. When the quantity of distal water freed exceeds a critical level, collecting duct reabsorption may fail to return the fluid to isotonicity and $T^{\circ}H_2O$ will fall to negativity (i.e. to CH_2O). In hydropenic dog, a sharp increase in distal sodium supply and reabsorption may thus provoke a prompt fall in measured $T^{\circ}H_2O$. The moderately lower $T^{\circ}H_2O$ and $T^{\circ}H_2O$ /GFR in the post-obstructive kidney in most experiments (Fig. 3) and the rapid fall in $T^{\circ}H_2O$ to increasing levels of CH_2O in other experiments (Fig. 4) are therefore both consistent with a marked increase in sodium supply to and transport by the distal nephron indicating reduced absorption by the proximal tubule.

The results presented in these studies are in contrast with those reported earlier from our laboratory using similar methods to evaluate the effects of a unilateral fall in GFR induced by acute partial constriction of one renal artery (10). After a Blalock clamp was applied to the right renal artery, mannitol was infused at increasing rates in either hydrated or hydropenic dogs as in the present protocol.

In the previously published studies, the fall in GFR after clamping resulted in decreased absolute and fractional sodium excretion. Enhanced sodium reabsorption in the proximal nephron with decreased sodium delivery to distal sites was suggested by decreases in CH_2O , CH_2O /GFR, and in $CNa + CH_2O$ /GFR as well as lower UNA/U_{osm} . Several differences between the constricted $T^{\circ}H_2O$ curves and the present postobstructive $T^{\circ}H_2O$ curves were apparent. In the constricted kidney there was a slower continuing rise in $T^{\circ}H_2O$ with a delayed plateau, while $T^{\circ}H_2O$ in the control kidney was simultaneously falling to negativity, i.e., to CH_2O (10). This indicated a relatively slower increase in distal sodium supply in the constricted kidney compared to the contralateral control. In the POK, as already noted, there was an early plateau in $T^{\circ}H_2O$ and in some studies a rapid fall to CH_2O while $T^{\circ}H_2O$ was increasing in the control kidney. This striking contrast with the constricted kidney is further suggestive of a more rapid increase in distal sodium supply and transport in the POK.

Two major proposals may explain the increase in fractional distal sodium supply, transport, and excretion in the postobstructive kidney. An adaptive increase in

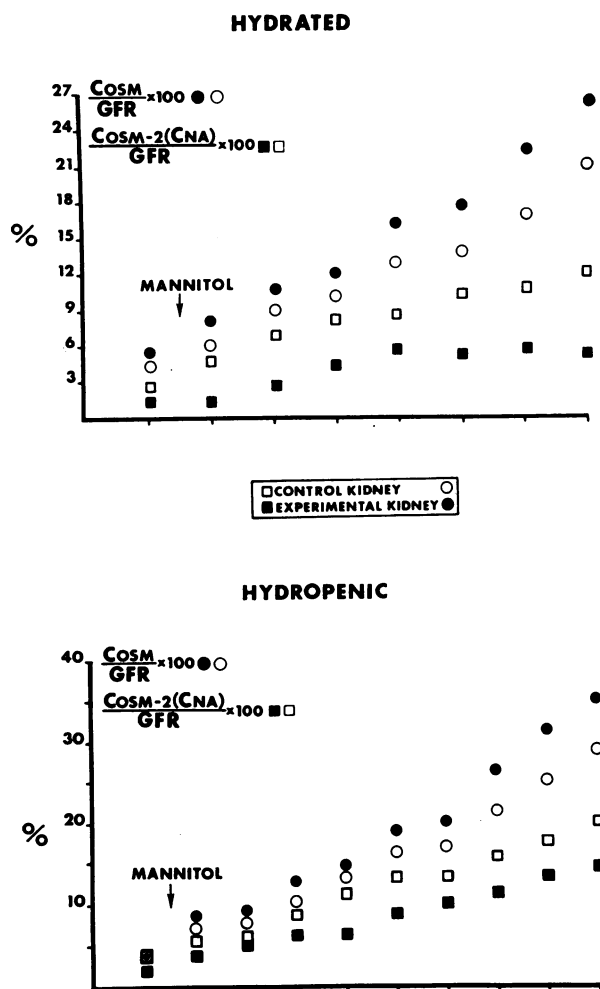


FIGURE 5 Cosm/GFR times 100 and Cosm-2(CNa)/GFR times 100 in postobstructive kidney and contralateral control in a hydrated and hydropenic experiment.

GFR/nephron may decrease fractional proximal sodium reabsorption (22). Alternately, ureteral obstruction may result in a proximal tubular defect which limits the capacity to establish a normal sodium gradient in the presence of nonreabsorbable solute without regard to the level of glomerular perfusion.

Three lines of evidence argue against the proposition that glomerular hyperperfusion may explain these findings. When the fraction of solute excretion attributable to salt is subtracted from total solute excretion and the remaining solute clearance related to GFR, the resultant expression, $Cosm-2(CNa)/GFR$, is consistently lower on the obstructed side (Fig. 5). This difference appears particularly evident at higher rates of solute excretion. Stated in other terms, the increase in fractional solute clearance ($Cosm/GFR$) on the postobstructive side seems entirely attributable to increased sodium and re-

lated anion (salt) excretion (Fig. 5). The rate of excretion of nonreabsorbable solute such as mannitol and other nonsalt solute in relation to GFR is never higher on the experimental side. An element of glomerular hyperperfusion would be expected to produce an increase in all the components of fractional solute excretion—mannitol and nonsalt solute, as well as salt—particularly at higher rates of mannitol infusion.

Secondly, glomerular hyperperfusion would be expected to result in glycosuria appearing in the experimental kidney before the control kidney. This did not occur in four glucose experiments in which there was an opportunity to observe initial glycosuria.

Finally, the relationship between the changes in GFR and glucose Tm's in the control and experimental kidney does not support the glomerular hyperperfusion proposal. In the experimental kidney, there occurred a consistent modest fall in glucose Tm compatible with some decrease in the number of operating nephrons (Table V). However, the simultaneous fall in GFR was proportionately greater in the postobstructive kidney (Table V). The consequent decrease in GFR/glucose Tm on the experimental side suggests a diminished glomerular perfusion per remaining functioning tubular mass. The reason for the difference between GFR/Tm glucose in these studies and the higher GFR/Tm PAH in the kidneys with chronic hydronephrosis reported by Suki et al. (8) is not apparent, but may result from the fact the obstruction in their animals was of longer duration.

It is difficult to be certain that the reduction in glucose Tm indeed reflects a reduced functioning nephron mass since there can be no assurance that the glucose load was sufficient to saturate tubular reabsorptive capacity. However the observation that blood glucose levels exceeded 400 mg per 100 ml in the periods with a low GFR and that glycosuria was present on the experimental side suggests that there was an adequate glucose load. It appears likely that a considerable fraction of the increment in GFR noted in some of the early transitional periods resulted from an increase in the number of functioning nephrons and tubular transport capacity. This may have resulted from the return to perfusion of glomeruli that had dropped out of the circulation during the period of obstruction. The stable GFR and Tm values observed during the steady-state phase of the study suggests that the number of nephrons functioning in the POK throughout the major portion of the experiment remained relatively constant.

These experiments suggest that 24 hr of ureteral obstruction in the dog limits the capacity of the proximal tubule to establish a gradient for sodium reabsorption during a mannitol infusion. Some of the studies, however, show a relative increase in distal sodium supply before the infusion of the mannitol load. Diminished frac-

tional proximal sodium reabsorption may thus develop without imposing an osmotic load and a sodium concentration gradient in the proximal tubule. The differences between both kidneys become sharper, however, during the mannitol infusion so that the decreased proximal reabsorption in the experimental kidney is more evident under these conditions.

These data do not exclude a simultaneous defect in distal sodium transport. It was noted earlier that K excretion, derived in large part from distal tubular secretion is sometimes lower in the POK when absolute sodium excretion is higher. This suggests the possibility that there is some impairment of distal tubular function notwithstanding the fact that an alternate explanation may be valid.⁴ Seely and Dirks have recently proposed that a major effect of mannitol in inhibiting sodium reabsorption may occur in the ascending limb of Henle's loop, at least in the hydropenic state (23). Although this observation has not yet been confirmed it is entirely possible that a portion of the augmented sodium excretion in the POK may derive from a site beyond the proximal tubule. The failure for absolute CH_2O on the experimental side to rise to those levels noted on the normal side when salt excretion is sometimes absolutely higher in the POK hints at some distal limit. It is difficult, however, to anticipate what fraction of the increased distal supply should be absorbed at rising flow rates. Any guess at the extent of a possible distal limit, therefore, seems hazardous.

Several of the major findings presented here such as increased fractional sodium and free water excretion, but diminished $\text{T}^*\text{H}_2\text{O}$ formation in the experimental kidney bear an interesting similarity to those reported by Bricker and his associates in some of their studies (24, 25). These workers produced a variety of unilateral renal lesions including pyelonephritis and aminonucleoside nephritis. Suki et al. also observed an increase in fractional salt and free water excretion in chronically hydronephrotic dogs (8). The functional similarity in this disparate group of pathological conditions suggests some common unifying feature. Since each pathological state was characterized by a significant loss of functioning nephrons, it may be speculated that this stimulus provokes an adaptive alteration in the residual nephrons by decreasing the sodium reabsorptive capacity of the proximal segment. Such a change in function, by enhancing distal sodium and water supply, would tend to limit progressive salt and water retention. It would also preserve some concentrating ability as well as considerable diluting capacity and would sustain relatively high rates of potassium, titratable acid, and ammonia excretion. The present studies suggest that such an adaptive mechanism may develop within 24 hr without any evident anatomic change.

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