Studies on the Control of Sodium Excretion in Experimental Uremia

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ABSTRACT A study of the mechanisms governing the high rate of sodium excretion per nephron characteristic of patients with chronic renal disease has been made in dogs. A "remnant kidney" was produced by 85% infarction of the left kidney while the right kidney was left intact. A bladder-splitting procedure allowed simultaneous measurement of glomerular filtration rate and the rate of sodium excretion by each kidney. The animals were fed a constant known amount of sodium chloride and 0.1 mg of 9 α -fluorohydrocortisone twice daily throughout the study.

In a group of dogs fed 3 or 5 g of salt per day, sodium excretion by the remnant kidney averaged 6.5 μ Eq/min while the intact kidney was present and 53.7 μ Eq/min when the animals became uremic after the intact kidney was removed. The increased sodium excretion per nephron by the remnant organ often occurred within 18 hr after contralateral nephrectomy and persisted despite experimentally induced acute reductions in the glomerular filtration rate to below pre-nephrectomy levels. A second group of animals studied in the same manner but receiving 1 g of salt per day or less failed to develop a natriuresis after contralateral nephrectomy despite high grade uremia. Thus an increased impermeable solute load per nephron was not a regulatory factor in the production of the natriuresis. The increased rate of sodium excretion per nephron in uremia resembles that after saline loading in that it may occur without an increase in glomerular filtration rate or a reduction in mineralocorticoid stimulation. It follows that an additional factor or factors must be involved in the genesis of the natriuresis.

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In contrast to the natriuresis that is seen in normal animals subjected to saline loading, these uremic animals were found not to have a detectable increase in extracellular fluid volume or blood volume in the presence of high fractional sodium excretion rates.

Sodium excretion in response to a small salt load by the remnant organ in uremia was 30% greater than the response of both kidneys in the preuremic state despite a markedly reduced total GFR. These data are consistent with the view that the volume control mechanism becomes more responsive in uremia.

INTRODUCTION

Patients with chronic renal disease generally are capable of maintaining sodium balance on an average salt intake despite a marked reduction in their functioning nephron population. It follows that if the range of salt intake remains uniform, sodium excretion per nephron must increase by approximately twofold for every 50% reduction in glomerular filtration rate (GFR). At very low levels of GFR, therefore, the fraction of filtered sodium excreted must be quite large. For example on a 7 g salt intake with a GFR of 4 ml/min, 16% of the filtered sodium must be excreted to maintain balance. Similar considerations indicate that the range over which both absolute sodium excretion per nephron and the fraction of filtered sodium excreted must change in response to relatively small changes in salt intake must become progressively larger as GFR becomes progressively lower.

The mechanisms responsible for the renal regulation of sodium excretion in uremia are only partially understood. The present studies are addressed to a further definition of these mechanisms.

METHODS

Studies were performed on female mongrel dogs weighing between 10–20 kg. A "remnant" kidney was produced in one kidney in each dog by ligating sufficient second and third

order branches of the left renal artery to reduce the renal mass by approximately 85%. The extent of the infarction could be established at the time of surgery by observing the area of ischemia. The residual nephrons, when examined at necropsy, were free of any pathologic stigmata of chronic disease except for limited round cell infiltration at the junction of the infarcted and noninfarcted zones. The dogs were allowed to recover from the surgical procedure for at least a week, after which the urinary bladder was divided into two permanent hemi-bladders in the manner described previously (1). An additional week was allowed for recovery from this procedure.

86 studies were performed on 27 dogs. Each of the animals was maintained on a constant caloric intake containing a known amount of salt throughout the duration of the studies (from 7 days to 6 wk). The basic diet contained less than 1 mEq of sodium per day. In all but one group of animals a weighed amount of sodium chloride was added to the diet. 0.2 mg of 9- α -fluorohydrocortisone also was given daily. The diet, the added sodium chloride (1, 3, or 5 g/day), and the mineralocorticoid hormone were administered by stomach tube twice daily in two equal parts. The animals were maintained on this regimen for a minimum of 5 days before experiments were begun. Several different types of experiments were performed.

Serial studies. (a) 3–5 g salt intake. Serial experiments designed to measure the changes in the patterns of sodium excretion by the remnant kidneys were performed in eight dogs maintained on either a 3 or a 5 g salt diet. From one to three control experiments were performed with the normal kidney *in situ*. Simultaneous measurements were made on both the remnant and the contralateral kidneys. Thereafter the normal kidney was removed surgically, and repeated experiments were performed on the remnant kidney over an 8 day period. In six of the eight dogs, the initial postnephrectomy study on the remnant organ was carried out within 18 hr of contralateral nephrectomy. (b) 0–1 g salt intake. In six animals serial studies were performed according to the above schedule; however, these dogs received either no supplementary salt or 1 g of supplementary salt.

Renal artery constriction. In six animals, the effects of renal arterial constriction on sodium excretion were studied approximately a week after the control kidney had been removed and uremia had developed. A constricting band was placed loosely about the renal artery of the remnant kidney 24–48 hr before the study. The experiments then were performed with the dogs awake and in the standing position. Several control clearance periods were obtained, after which the band was constricted so as to reduce GFR and filtered load of sodium below the level observed in the pre-nephrectomy control studies in the same kidney.

Timed response to a 2.5 g salt load. A series of studies was performed to determine the quantitative response of the remnant kidneys. A total of 31 studies was performed on 13 dogs. Each animal was maintained chronically on a 5 g salt diet in the manner described above. On the morning of study, one-half of the daily salt load (2.5 g) was administered in one of four different ways: (a) intravenously as isotonic saline at 5 ml/min; (b) intravenously as isotonic saline at 50 ml/min; (c) by stomach tube as isotonic saline (the low-salt basic diet was omitted in these experiments); (d) by stomach tube as sodium chloride dissolved in 250 ml of water together with half of the basic daily diet. In all dogs the effects of at least two different routes of administration were examined both before and after removing the normal

kidneys. In the typical study, the infusion for the measurement of creatinine clearance was initiated approximately 2 hr before administering the salt load. Three to four preliminary clearance periods were obtained to determine the base line patterns of sodium excretion. Thereafter the salt load was delivered and the excretion of sodium was determined during five successive 1-hr periods. GFR was measured during each of the urine collection periods. The patterns of sodium excretion during the 5 hr after administration of the salt load in the postnephrectomy studies were compared with those in the pre-nephrectomy control studies. Comparisons also were made between the response to the various routes of administration of sodium chloride. In all of these studies, the animals were awake and standing quietly in a supporting sling. The sodium load was administered at the same time of day in all studies in individual dogs.

Studies of inulin space. In nine animals maintained on a 5 g salt diet, extracellular fluid volume was estimated before and after removing the normal kidney. Inulin space was measured using the method of Deane (2). GFR and sodium excretion were determined simultaneously with the measurements of inulin space.

Red cell mass and blood volume. In five of the animals in which inulin space was determined, simultaneous measurements were made of blood volume with ^{51}Cr -labeled red blood cells from the same animal (3).

In all studies, GFR (exogenous creatinine clearance), filtered load of sodium, and sodium excretion rates were determined. 7–10 ml of blood were collected at the midpoint of each period through a catheter placed in the external jugular vein. Infusions were delivered via a peripheral vein generally in a hind limb. Creatinine dissolved in 5% dextrose in water was delivered at a rate of 3 ml/min in the pre-nephrectomy studies and 1 ml/min in postnephrectomy studies. Creatinine was determined according to the method of Bonsnes and Taussky (4). Sodium was measured on a flame photometer. When serial studies were performed, the red blood cells obtained during each clearance period were reconstituted to the original hematocrit with isotonic saline and returned at the end of each experiment.

RESULTS

In Table I are shown the results of pre-nephrectomy control values for GFR and sodium excretion on normal and remnant kidneys in 18 dogs used in the serial studies. Six dogs were maintained on a 5 g salt diet, six on a 3 g salt diet, and six on 1 g of salt per day or less. GFR for the normal kidneys ranged from 30.5 to 81 ml/min. Values for the remnant kidneys ranged from 3.6 to 11.1 ml/min. The fraction of filtered sodium excreted was slightly greater for the remnant than for the control kidneys in all but one of the dogs. Nevertheless, all of the remnant kidneys reabsorbed at least 98.5% of the filtered sodium, and in 14 of the 18 dogs, sodium reabsorption exceeded 99% of the filtered load.

Serial studies. The results of five successive studies on a representative dog maintained on a 5 g salt diet are shown in Table II. Values are recorded for the remnant kidney only. During the pre-nephrectomy study, the sodium excretion rate averaged 6.0 $\mu\text{Eq}/\text{min}$. The normal kidney excreted an average of 56.1 $\mu\text{Eq}/\text{min}$ during

TABLE I
Summary of Control Measurements of Dogs in Serial Studies

No. of dogs	Diet	GFR		U _{Na} V		U _{Na} V/FL _{Na}	
		I	R	I	R	I	R
		<i>ml/min</i>		<i>μEq/min</i>		<i>%</i>	
12	3 or 5 g NaCl	58.0(SE) ± 3.6	6.4(SE) ± 0.5	24.5(SE) ± 4.2	7.2(SE) ± 0.8	0.34(SE) ± 0.07	0.85(SE) ± 0.10
6	0.25 or 1 g NaCl	55.3 ± 6.1	8.4 ± 0.9	6.5 ± 1.6	4.1 ± 0.9	0.10 ± 0.02	0.39 ± 0.58

Values represent means ± standard error.

GFR, glomerular filtration rate; I, intact kidney; R, remnant kidney; U_{Na}V, sodium excretion rate; U_{Na}V/FL_{Na}, fractional sodium excretion.

this study. 18 hr after removing the normal kidney, the GFR of the remnant organ had increased from an average pre-nephrectomy value of 6.1 to 8.0 ml/min. At the same time the sodium excretion rate had risen to 50 μEq/min. The fraction of filtered sodium excreted increased from an average pre-nephrectomy value of 0.7 to 4.7%. In the three subsequent studies performed on days 2, 3, and 6, GFR remained between 7 and 7.8 ml/min, sodium excretion rate varied from 61 to 87 μEq/min, and fractional sodium excretion increased further to 8%.

The results of the serial studies on all eight dogs maintained on the 3 or 5 g NaCl diets are summarized in Table III. In four of the six dogs which were studied within 18 hr of removing the normal kidney, sodium excretion rates by the remnant kidney increased by at least threefold. In studies performed from the 2nd through the 8th postnephrectomy day substantial increases in sodium excretion by the remnant kidneys occurred in all eight dogs. In most animals, GFR and the filtered load of sodium increased. However in two animals (dogs 6 and 7) GFR and filtered sodium decreased modestly. The natriuresis occurred nevertheless. All ani-

mals exhibited an appreciable increase in the fraction of filtered sodium excreted. The average blood urea nitrogen (BUN) on the final day of study in this group was 77 mg/100 ml.

In order to examine the role of the increase in GFR on the increased rates of sodium excretion by the remnant kidneys, the effects of reduction of GFR by constriction of the renal artery were measured. The data from the six dogs subjected to this procedure are recorded in Table IV. Values are shown for the pre-nephrectomy control study, as well as for the post-nephrectomy experiment before and after constricting the renal artery. In three of the six dogs no evidence of an increase in GFR was observed in the postnephrectomy state. Conceivably this may have related to some degree of arterial constriction created by the band even before experimental constriction. Yet each of these dogs exhibited a typical increase in sodium excretion in the postnephrectomy study. In one animal (dog No. 9), GFR and urine flow were sufficiently reduced that further constriction was not carried out. In all six animals, sodium excretion rate in postnephrectomy studies had increased markedly over pre-nephrectomy values; and with constriction, excretion rates remained well above the corresponding values in the pre-nephrectomy studies despite the fact that the filtered load of sodium was from 15 to 48% lower.

One factor that could contribute to the acquired natriuresis by the remnant kidneys is an increase in the filtration of impermeable or poorly permeant solutes which can accumulate in the extracellular fluid in uremia. This possibility was examined in two ways. The first involves the study of dogs maintained on a low sodium diet (1.0 g of NaCl or less). Data from this group of experiments are summarized in Table V. Sodium excretion rate by remnant kidneys averaged 4.1 μEq/min and by the remnant plus control kidneys averaged 10.7 μEq/min in the pre-nephrectomy studies. In the postnephrectomy studies, the excretion rates by the remnant kidneys averaged only 13.1 μEq/min despite the existence of chemical abnormalities of uremia. Two postnephrectomy studies

TABLE II
Representative Experiment in Which the Sodium Excretion of the Remnant Kidney Was Followed for 6 Days after Contralateral Nephrectomy*

Day	Weight	BUN	GFR	FL _{Na}	U _{Na} V	U _{Na} V/FL _{Na}
	<i>kg</i>	<i>mg/100 ml</i>	<i>ml/min</i>	<i>μEq/min</i>	<i>μEq/min</i>	<i>%</i>
Control	12.4	10.0	6.1	819	6	0.7
Intact kidney removed						
18 hr	12.5	31.0	8.0	1069	50	4.7
2	12.7	52.5	7.0	984	51	6.2
3	12.5	54.0	7.8	1101	81	7.9
6	11.8	63.0	7.1	995	76	7.7

* Experiment performed on dog No. 8.

BUN, blood urea nitrogen. All other abbreviations are explained in Table I.

TABLE III
Summary of Studies on the Remnant Kidney of Dogs

Dog No.	Pre-nephrectomy					Post-nephrectomy		
	GFR	FLNa	UNaV	UNaV/FLNa	BUN	GFR	FLNa	UNaV
	ml/min	$\mu\text{Eq}/\text{min}$	$\mu\text{Eq}/\text{min}$	%	mg/100 ml	ml/min	$\mu\text{Eq}/\text{min}$	$\mu\text{Eq}/\text{min}$
1	3.58	425	7.1	1.47	14	4.27	561	28.4
2	4.35	583	7.8	1.32	14	5.64	784	27.3
3	5.94	804	3.4	0.54	7	7.21	1004	13.6
4	7.13	975	7.0	0.73	12	7.96	1010	6.0
7	5.75	754	9.0	1.26	9	6.45	877	12.2
8	5.58	819	5.9	0.75	10	7.96	1069	49.8
5	5.32	767	3.7	0.45	10			
6	9.50	1288	7.9	0.59	12			

See Table I for explanation of all abbreviations.

* Values represent average of all experiments performed on days noted.

were performed in each of the animals, and no tendency for sodium excretion rates to increase with time was observed despite the fact that the BUN values during the second studies ranged from 61 to 150 mg/100 ml (mean 87.5 mg/100 ml). In the dogs maintained on 3 or 5 g salt diet, sodium excretion rates by the remnant kidney averaged 48.9 $\mu\text{Eq}/\text{min}$ with an average BUN of 69 mg/100 (Table III). Dogs in the low sodium group lost an average of 1.1 kg in the 8 day period of study, while dogs on the higher sodium intake lost an average of 0.9 kg in the same period. Thus despite the presence of the chemical abnormalities of uremia, sodium excretion increased only minimally when the salt intake was restricted.

The second technique employed to examine the effects of retained solute on the natriuresis involves the study of sodium excretion within 18 hr of removal of the normal kidney, an interval too short to allow for appreciable retention of impermeable solutes. These data which are summarized in Table III have already been discussed. In four of the six dogs, natriuresis evolved although the average BUN for these four dogs was only 31.5 mg/100 ml.

Inulin space and blood volume were measured first with both the intact and remnant organs present and again 5-8 days after removal of the intact organ. Composite data are listed in Table VI. The rates of sodium excretion for the remnant kidneys are included in this table. The mean extracellular fluid volume as estimated by the inulin space was slightly less in the postnephrectomy than in the pre-nephrectomy studies. However, the mean weight of the animals also decreased (from 16.7 to 15.6 kg) and when the extracellular fluid (ECF) volume was expressed as a per cent of body weight the respective values were 19.2 vs. 18.8. The two values do not differ significantly. Values for blood volume also

decreased modestly in the postnephrectomy state, but when expressed as a per cent of body weight, the pre-nephrectomy vs. postnephrectomy values were 10.5 and 10.4% respectively. These values also are not significantly different. The changes in sodium excretion rates in these nine dogs were comparable to those observed in the other animals on the same salt intake. Thus the average excretion rate for sodium by the remnant kidneys was 4.1 $\mu\text{Eq}/\text{min}$ in the pre-nephrectomy studies and 31.7 $\mu\text{Eq}/\text{min}$ in the postnephrectomy studies. 0.5% of the filtered sodium was excreted in the pre-nephrectomy studies and 3.9% in the postnephrectomy studies.

Studies of the sensitivity of the control system. The natriuretic response of the remnant kidney to the administration of 2.5 g of sodium chloride via four different routes were studied in 13 dogs before and after removing the normal kidney. A total of 31 experiments was performed. Before study these animals had been maintained on a constant intake of salt (5 g/day) and mineralocorticoid hormone in the manner described above. On the morning of study, control measurements were obtained to determine the base line rate of sodium excretion and GFR. Thereafter, the loading dose of sodium chloride was administered and measurements were continued at hourly intervals for 5 hr.

A representative study is presented in Table VII. In the pre-nephrectomy study, both the remnant and the normal kidneys increased sodium excretion after the administration of the 2.5 g salt load. Over the 5 hr interval, the remnant kidney excreted 1956 μEq of sodium and the normal kidney, 8070 μEq of sodium. These values represent an increase over the projected excretion rate (calculated as the excretion rate per hour before the administration of salt load multiplied $\times 5$) of 1211 and 4830 μEq . Fractional sodium excretion rose from 0.37 to 1.30% in the remnant kidney. A comparable

(18 hr)		Postnephrectomy* (2nd-8th day)					Days observed
UNaV/FLNa	BUN	GFR	FLNa	UNaV	UNaV/FLNa	BUN	
%	mg/100 ml	ml/min	$\mu\text{Eq}/\text{min}$	$\mu\text{Eq}/\text{min}$	%	mg/100 ml	
5.05	40	4.39	597	79.1	12.60	81	2-4
3.50	36	5.77	813	53.2	6.55	66	2
1.33	19	7.05	988	56.2	5.60	81	2-5,8
0.41	36	7.55	1067	38.6	4.49	86	2-8
1.37	23	4.34	608	56.5	9.32	73	2,3,6,8
4.43	31	6.78	1040	47.2	6.31	73	2,3,6
		7.76	1053	65.6	5.95	68	3-5,8
		8.66	1171	32.0	3.20	47	2,3,5

change occurred in the normal organ. Maximal excretion occurred in the 3rd hr bilaterally.

The same salt load was administered via the same route after the control kidney had been removed. Sodium excretion rate in the 5 hr interval after administering the load was greater than the combined excretion rate of remnant plus the normal kidney in the pre-nephrectomy studies. The increase over the projected excretion rate was slightly less than the combined two kidney values in the pre-nephrectomy studies. Fractional sodium excretion increased from an initial level of 2.43 to a maximum of 6.41%. Maximum sodium excretion occurred in the 3rd hr. Thus in response to the same salt load, the remnant kidney excreted more sodium both in absolute terms and in terms of the increase over projected base line excretion rates in the uremic state than when the contralateral control kidney contributed to function.

Table VIII presents the data from the 31 observations in the 13 dogs. The combined 5 hr sodium excretion rates for remnant plus control kidneys in the pre-nephrectomy studies was 8914 μEq . The 5-hr value for the remnant kidney alone in the postnephrectomy studies was 11,705 μEq . For the group the difference between the 5-hr excretion rate and the projected 5-hr excretion rate was 3900 μEq for the two kidneys in the pre-nephrectomy studies and 2100 μEq for the remnant alone in the post-nephrectomy studies. This occurred despite the fact that the GFR in the remnant kidney in the postnephrectomy studies averaged only 15% of the total (i.e. combined two kidney) GFR in pre-nephrectomy studies. The route of sodium administration did not affect the response, and there was no difference for either individual animals or group data between slow intravenous infusion (11 experiments), rapid intravenous infusion (six experiments), intragastric saline instillation (seven ex-

TABLE IV
Summary of Data from the Constriction Experiments: Glomerular Filtration Rate, Filtered Sodium, and Sodium Excretion by the Remnant Kidney

Dog No.	Pre-nephrectomy			Postnephrectomy			Postnephrectomy with constriction		
	GFR	FLNa	UNaV	GFR	FLNa	UNaV	GFR	FLNa	UNaV
	ml/min	$\mu\text{Eq}/\text{min}$	$\mu\text{Eq}/\text{min}$	ml/min	$\mu\text{Eq}/\text{min}$	$\mu\text{Eq}/\text{min}$	ml/min	$\mu\text{Eq}/\text{min}$	$\mu\text{Eq}/\text{min}$
4	7.13	975	6.99	6.96	1029	86.7	5.72	832	37.5
5	5.32	767	3.69	5.38	716	114.0	4.01	524	56.5
10	8.68	1180	11.2	11.0	1528	55.9	6.76	903	17.6
11	5.55	760	3.74	7.38	1022	77.0	5.28	708	29.4
							4.80	628	18.6
12	7.05	967	7.43	8.64	1150	88.3	4.41	575	39.4
							3.90	498	29.4
9	8.53	1117	11.8	5.59	729	25.3			

See Table I for explanation of all abbreviations.

TABLE V
Sodium Excretion by the Remnant Kidney of Dogs Fed a Low Salt Diet

Pre-nephrectomy								Post-nephrectomy						
Dog	NaCl	GFR	FL _{Na}	U _{Na} V	U _{Na} V/ FL _{Na}	BUN	Wt	Day	GFR	FL _{Na}	U _{Na} V	U _{Na} V/ FL _{Na}	BUN	Wt
	g/day	ml/min	μEq/min	μEq/min	%	mg/100 ml	kg		ml/min	μEq/min	μEq/min	%	mg/100 ml	kg
13	0.25	7.37	944	1.82	0.19	18	15.2	3	6.71	911	5.6	0.63	69	14.1
								6	5.16	692	11.9	1.65	98	13.6
14	0.25	8.47	1101	7.18	0.64	22	15.9	3	8.71	1191	11.9	1.00	88	15.4
								6	7.15	979	5.9	0.57	105	15.2
16	0.25	11.1	1430	2.91	0.16	14	15.9	5	12.3	1749	14.5	0.82	60	15.9
								7	12.5	1731	2.7	0.13	61	15.6
17	0.25	5.20	677	2.04	0.34	10	18.8	5	5.30	739	18.8	2.55	91	17.9
								7	5.35	723	12.6	1.66	108	18.2
15	1.00	7.38	945	5.17	0.52	15	13.9	2	7.42	1007	8.0	0.80	56	13.7
								5	4.02	543	14.4	2.18	150	12.8
18	1.00	10.3	1383	5.37	0.39	18	14.3	2	12.4	1790	19.5	1.05	39	14.4
								4	15.9	2330	13.1	0.62	76	14.5

See Table I for explanation of all abbreviations.

periments), or intragastric feeding of sodium chloride mixed with water and food (seven experiments).

When the excretion rate of the remnant kidneys in the postnephrectomy studies is compared with the values for only the remnant kidneys in the pre-nephrectomy studies, the change is very dramatic. Thus after nephrectomy, the same kidneys excreted more than five times as much sodium in the same time interval after the same salt load given by the same route.

DISCUSSION

In the present studies we have considered five factors that could increase sodium excretion rate per nephron in uremia. These include: (a) disease of tubules with a subsequent reduction in the capacity to reabsorb filtered sodium; (b) decreased mineralocorticoid hormone stimulation limiting the capacity of the surviving nephrons to reabsorb sodium; (c) the retention and filtration of poorly reabsorbable solutes; (d) an adaptive increase

TABLE VI
Inulin Space and Blood Volume Compared with Sodium Excretion by the Remnant Kidney before and after Development of Uremia

Dog No.	Inulin space				Blood volume				Sodium excretion by remnant kidney			
	Control		Uremia		Control		Uremia		U _{Na} V		U _{Na} V/FL _{Na}	
									Control		Uremia	
	liters		% body wt		liters		% body wt		μEq/min		%	
10	4.34	3.84	25.8	24.1	1.83	1.76	10.5	10.9	7.5	29.6	0.75	2.37
12	3.94	3.22	25.2	22.8	1.68	1.66	11.2	11.3	4.6	20.6	0.64	2.17
21	2.76	2.46	17.8	17.5	1.30	1.22	8.4	8.6	2.9	29.8	0.20	1.76
23	4.42	4.37	19.5	20.4	2.52	2.24	10.8	10.7	5.0	48.7	0.52	5.20
24	4.16	3.42	19.4	17.0	2.30	2.20	11.5	10.5	2.6	49.3	0.53	0.40
11	3.09	2.67	22.6	22.4					4.0	46.0	0.76	6.81
19	2.25	2.09	14.9	15.2					4.7	32.6	0.66	3.70
20	1.53	1.41	11.5	11.8					2.9	19.6	0.40	2.43
22	2.58	3.05	15.9	18.3					2.4	8.8	0.15	0.55
Means	3.23	2.95	19.2	18.8	1.93	1.81	10.5	10.4	4.1	31.7	0.51	3.93

See Table I for explanation of abbreviations.

TABLE VII
Representative Experiment of Response of a Dog to a Small Salt Load before and after the Development of Uremia

Hour	Control						Uremia		
	Intact kidney			Remnant kidney			Remnant kidney		
	GFR	UNaV	UNaV/ FLNa	GFR	UNaV	UNaV/ FLNa	GFR	UNaV	UNaV/ FLNa
	<i>ml/min</i>	<i>μEq/hr</i>	%	<i>ml/min</i>	<i>μEq/hr</i>	%	<i>ml/min</i>	<i>μEq/hr</i>	%
Control	44.5	648	0.19	5.3	149	0.37	6.2	1176	2.43
	2.5 g of NaCl given by gastric tube with food								
First	45.3	490	0.17	5.6	115	0.32	6.4	1134	2.22
Second	44.0	1110	0.32	5.5	300	0.69	7.0	1680	2.92
Third	44.3	2670	0.64	5.2	493	0.99	6.7	3348	6.41
Fourth	40.4	1994	0.64	4.6	463	1.30	6.7	2562	4.97
Fifth	40.7	1806	0.57	4.6	436	1.22	6.4	1670	3.23
5 hr total		8070			1956			11394	
Expected total*		3240			745			5880	
Difference		4830			1211			5514	

See Table I for explanation of all abbreviations.

* Value obtained by multiplying excretion rate in control hour by 5.

in GFR per nephron; and (e) a regulated reduction in fractional reabsorption of filtered sodium by the renal tubules, largely unrelated to any of the foregoing factors.

The experiments were designed to differentiate between these events. Each of the dogs studied had one kidney with a markedly reduced nephron population and a contralateral control organ, with a normal complement of nephrons. Both sodium intake and caloric intake were maintained constant throughout the periods of study. The patterns of sodium excretion by the remnant kidneys were studied first with the contralateral normal kidney *in situ*. Then the normal kidney was removed and the transformation that took place in the residual nephrons of the remnant kidney was observed often in serial fashion as uremia evolved. The opportunity thus existed to compare sodium excretion by the same nephrons in the same animals first under conditions wherein the total nephron population exceeded 60% of the original number, then under conditions where the total nephron population approximated 10–20% of the original

number. The patterns of sodium excretion changed in a fashion that was both striking and appropriate for the maintenance of sodium balance. The data provide some insight into which the possible contributory factors may have served in a primary role in the functional changes.

The experimental model precludes the contribution of damaged residual nephrons to the genesis of the natriuresis per nephron. The experimental kidneys were "remnant" organs, and there was no apparent intrinsic renal disease in the surviving nephron population. The experimental design also excludes the contribution of mineralocorticoid insufficiency in that each of the dogs was maintained on a large dose of a potent salt-retaining steroid throughout the period of study. The contribution of a sustained natriuresis mediated by poorly reabsorbable solutes is more difficult to examine directly, but two observations suggest that this mechanism probably was not the key factor in the genesis of the natriuresis. The first observation is that the natriuresis began within 18 hr of removal of the normal kidney, an interval too short to allow for substantial retention of poorly reab-

TABLE VIII
Summary of 31 Experiments of the Type Depicted in Table VII

	Control			Uremia
	Intact kidney	Remnant kidney	Total	Remnant kidney
UNaV, <i>μEq/5hr</i>	6954(SE) ± 1193	1960(SE) ± 189	8914(SE) ± 1323	11705(SE) ± 759
Expected*	3524 ± 384	1468 ± 118	4092 ± 510	9575 ± 765
Difference	3430 ± 894	492 ± 146	3922 ± 1016	2130 ± 533

* Value obtained by multiplying excretion rate in control hour by 5.

sorbable solutes. The second observation is that the retention of such solutes *per se* was not associated with a natriuretic effect in animals maintained on a low salt diet. Thus an increase in sodium excretion per nephron occurred before the overt retention of impermeable solutes when salt intake was maintained at 3–5 g/day and marked natriuresis per nephron did not occur despite overt solute retention when the salt intake was restricted. We would favor the view, therefore, that while poorly reabsorbable solutes may contribute to an increase in sodium excretion rate per nephron in uremia, a *regulated* natriuresis was probably not dependent upon such a mechanism; nor would such a mechanism appear to allow for the type of regulatory ability that the chronic uremic patient possesses in altering sodium excretion rates in accordance with sodium intake (5).

An adaptive increase in GFR per nephron could well increase the excretory capacity for sodium in surviving nephrons, and it is of interest that GFR did increase in the remnant kidneys in most animals after contralateral nephrectomy. Yet, the increase in GFR was not universal, and the natriuresis appeared in those animals in which GFR did not increase as well as in those in which hyperfiltration did develop. Moreover, when GFR per nephron was reduced acutely in the remnant kidneys of uremic animals, sodium excretion rates remained appreciably higher than the values observed in the same kidneys in pre-nephrectomy studies. A third observation may be relevant: in several animals maintained on a low salt diet, GFR increased but the natriuresis was substantially smaller than in the dogs maintained on a higher salt intake. Thus, hyperfiltration could well contribute to the capacity of the residual nephrons to increase the rate of sodium excretion; but natriuresis can occur without it and need not occur with it. Therefore it seems unlikely that hyperfiltration is the key modulating event in the control system for sodium excretion in uremia. Two recent studies have provided evidence that is consistent with this interpretation. In both, GFR was increased without a concomitant alteration in ECF volume. Lindheimer, Lalone, and Levinsky raised GFR in normal dogs by up to 30% either by feeding of high protein meal, administering glucocorticoids, or infusing dopamine (6). Sodium excretion rates increased only slightly, and fractional sodium excretion rates changed little. Slatopolsky, Elkan, Weerts, and Bricker raised GFR acutely in uremic patients (5) and in normal individuals (7) by infusing parathyroid hormone. Although filtered load of sodium increased by an average of 20.4 and 18.9% in uremic patients and normal individuals respectively, sodium excretion rates increased modestly, and fractional sodium excretion remained essentially unchanged. In the present studies, fractional sodium excretion increased from an average of 0.89 to

6.75% in the remnant kidney of dogs receiving 3–5 g of NaCl per day.

The evidence, therefore, points to the modulation of tubular reabsorption of sodium by a mechanism unrelated to any of the foregoing factors. Phenomenologically, the natriuresis has characteristics in common with the natriuretic response to saline loading. As was first shown by De Wardner, Mills, Clapham, and Hayter (8) and subsequently confirmed in many laboratories, the natriuresis after acute saline loading is not dependent on either an increase in GFR or a decrease in mineralocorticoid stimulation. Similarly in the present dogs, the increase in sodium excretion rate by the remnant kidneys produced by the removal of the contralateral normal organs did not require either an adaptive increase in GFR or a decrease in mineralocorticoid hormone activity. The natriuresis attendant upon both saline loading in normal animals and nephron reduction in animals on a modest salt intake is an appropriate response for the preservation of sodium balance and ECF volume. The question therefore must be asked as to whether the marked natriuresis in the remnant kidneys of the uremic models relates to chronic expansion of either ECF volume or of blood volume. The present studies do not support either of these possibilities. Within the limits of the methods used, neither ECF volume (inulin space) nor blood volume was greater in the uremic state than in the pre-nephrectomy control studies in the same animals, although sodium excretion by the remnant kidneys was increased by over 700%. Theoretically a homeostatic mechanism requires some displacement from the “normal” state in order to effect a change in end organ response; in the case of the volume control system in the uremic animals, this displacement appears to be very slight if the afferent limb detects an alteration in ECF or blood volume. The failure to detect an increase in blood volume or inulin space in the uremic dogs might also suggest that the control system continues to operate with striking efficiency.

In comparing the response of the remnant kidneys to a fixed load of sodium chloride given by four different routes of administration, the natriuresis was increased greatly in the uremic vs. the pre-nephrectomy state. Thus the nephrons of the remnant kidneys excreted four times as much sodium in the same time interval and after the same amount of salt when the normal kidney was absent than when it was present and contributing to urine formation. Indeed, the remnant kidney excreted more sodium than the remnant and the normal kidneys combined had excreted in the same animals before nephrectomy. When the timed response over the 5 hr interval was compared, no lag period was observed in the excretion response of the remnant kidney in the uremic state. Thus it cannot be assumed that the ex-

cretion lagged behind such that the stimuli to increased excretion multiplied over the 5 hr interval.¹ Rather however, from the present data, as well as those from uremic man (5), it would seem that as steady-state GFR decreases due to a permanent reduction in nephron population, the total system becomes more sensitive and more responsive to a given displacement from the steady state. The expression of this change is an enhanced response of the individual nephrons to a given load of sodium. It is unclear whether this enhancement involves an increased sensitivity of the detector mechanisms of the volume control system in uremia, a greater responsivity of the efferent mechanisms to a given displacement from the steady state, or to an exaggerated end organ response to a given efferent stimulus.

A number of different events have been shown to influence sodium excretion under specific experimental circumstances. During saline loading fractional reabsorption of sodium in the proximal tubule diminishes strikingly. Martino and Earley have presented evidence that physical factors may play a role in this suppression (9). Among these physical factors are decreased renal vascular resistance, a decreased plasma protein concentration, and increased renal perfusion pressure. Lewy and Windhager have presented evidence that peritubular oncotic pressure will influence proximal sodium reabsorption and have suggested that changes in filtration fraction by virtue of the associated changes in peritubular capillary protein concentration may exercise an influence over the rate of sodium reabsorption (10). Biochemical factors also may contribute to the natriuresis of saline loading. Recently Waugh and Kubo have shown that when substrates normally utilized by the kidney are added in small amounts to the infused saline, natriuresis is blunted (11). Finally, there is evidence from several sources that a humoral material with natriuretic capacity appears in the plasma of saline-loaded animals (8, 12, 13). The natriuresis of saline loading also appears to involve inhibition of sodium reabsorption beyond the proximal tubule. However, to date, the mechanisms involved in this inhibition remain to be elucidated.

Which of the foregoing mechanisms is responsible for the natriuresis of nephron reduction and for the enhanced sensitivity of the control system is not established by the

¹The base line sodium excretion rates were higher in the postnephrectomy than in the pre-nephrectomy studies on the same dogs. The apparent explanation for this is that the diurnal rhythm for sodium excretion was altered in the uremic state. Thus in serial measurements of sodium excretion made over 24-hr intervals, an increase in excretion rate occurred between 1 and 4 a.m. in the pre-nephrectomy studies, but not in the postnephrectomy studies.

present observations. It seems unlikely, however, that dilution of plasma proteins or of substrate plays a role since the amounts of saline administered were small and the same load of salt was administered before and after the development of uremia. Preliminary observations suggest that blood pressure does not change consistently after removing the normal organ, and data also of a preliminary nature suggest that no changes in cardiac output occur. The relative contribution of a change in the activity of a natriuretic hormone vs. changes in physical factor(s) within the renal interstitium remain for future investigation.

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