Studies on the Characteristics of the Control System Governing Sodium Excretion in Uremic Man

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ABSTRACT Sodium excretion was studied in a group of patients with chronic renal disease, (*a*) on constant salt intakes of varying amounts with and without mineralocorticoid hormone administration and, (*b*) after acute extracellular fluid volume expansion. The lower the steady-state glomerular filtration rate (GFR), the greater was the fraction of filtered sodium excreted on both a 3.5 and 7.0 g salt diet; and the lower the GFR, the greater was the change in fractional excretion in the transition from the 3.5 to the 7.0 g salt diet. This regulatory capacity did not appear to be influenced by mineralocorticoid hormone administration. After acute expansion of extracellular fluid (ECF) volume, the increment in sodium excretion exceeded the concomitant increment in filtered sodium in six of nine studies and in the remaining three studies, the increment in excretion averaged 59% of the Δ filtered load (i.e., only 41% of the increase in filtered sodium was reabsorbed). During saline loading, the decrease in fractional reabsorption of sodium tended to vary inversely with the steady-state GFR, although all patients received approximately the same loading volume. When an edema-forming stimulus was applied during saline infusion, the natriuretic response was aborted and the lag time was relatively short. When GFR and the filtered load of sodium were increased without volume expansion, the Δ sodium excretion averaged only 19% of the Δ filtered load; moreover, changes in fractional sodium reabsorption were considerably smaller than those observed during saline loading. The data implicate the presence of a factor other than GFR and mineralocorticoid changes in the modulation of sodium excretion in uremic man.

INTRODUCTION

It is unusual for a patient with chronically progressive renal disease either to accumulate edema or to sustain net sodium loss on an average salt intake. If this clinical observation reflects a continuing ability to maintain external sodium balance in the face of a diminishing number of functioning nephrons, sodium excretion/nephron must increase with time. Moreover, if external sodium balance is maintained on an unrestricted salt intake, the range over which sodium excretion varies in single nephrons must increase progressively as the nephron population decreases if ordinary day-to-day variations in salt intake are to be accommodated. Thus, to effect a change in total sodium excretion of any given magnitude, the average change in excretion *per nephron* must vary inversely with the number of nephrons. If this requirement for exaggerated changes in sodium excretion (per nephron) is fulfilled in chronic renal disease, an unusual opportunity might exist to distinguish tubular from glomerular contributions to the regulation of sodium excretion.

In the present study some aspects of the control of sodium excretion have been studied in uremic patients.

Dr. Ivan O. Elkan is a Research Associate at the John Cochran Veterans Administration Hospital. Dr. Neal S. Bricker is a recipient of a U. S. Public Health Service Career Research Award.

Received for publication 5 June 1967 and in revised form 1 November 1967.

METHODS

Studies were performed on 17 patients with chronically progressive renal disease. Eight had chronic glomerulonephritis, six chronic pyelonephritis, and three polycystic renal disease. Glomerular filtration rate (GFR) ranged from 1.2 to 63 ml/min. Studies also were performed on two normal volunteers. All of the subjects were informed of the experimental nature of the studies and each participated willingly. Several different protocols were followed.

Sodium excretion with different levels of salt intake. Patterns of sodium excretion were investigated in eight patients with chronic renal disease and in two normal individuals on the wards of the Clinical Research Center. All of the patients subsisted on both a 3.5 g and a 7.0 g salt diet; in selected studies, 250 mg and 10 g salt diets also were employed. Each diet was maintained for a minimum of 5 days and sodium intake was regulated in the following manner. The basic daily diet contained 2 g of NaCl. To this diet, each subject added a weighed quantity of NaCl calculated to bring the 24-hr intake to the desired level. The patients were instructed to use all of the salt and to eat all of the food to which salt was added. Any nonsalted food left was weighed and corrections were made in computing the sodium intake. When the deviations were appreciable, the dietitian, who supervised the patients closely, encouraged them to ingest an additional amount of salt sufficient to bring the total intake to the prescribed level.

Observations were made with and without chronic administration of 0.2 mg of 9-alpha-fluorohydrocortisone daily. When this drug was administered, it was begun at least 5 days before initial measurements were made. Sodium excretion was determined on 24-hr urine collections at least twice during each dietary regimen and the values were averaged for the balance computations. Clearance studies were performed after a given salt intake had been in effect for a minimum of 4 days. The priming and sustaining solutions used in the clearance studies contained no NaCl and the sustaining solution was delivered at a rate of 2 ml/min to avoid expansion of extracellular fluid volume.

Acute expansion of extracellular fluid volume. Studies on the effects of ECF volume expansion were performed with a hypotonic solution containing 90 mM NaCl and 60 mM glucose, 0.2 mg of 9-alpha-fluorohydrocortisone, 10 mg of desoxycorticosterone acetate (DOCA), and 3 U of pitressin tannate in oil were administered routinely in the morning before beginning the infusion. In each patient, three or more control clearance periods were obtained. Thereafter ECF volume was expanded. 1½–2 liters of hypotonic saline were infused over an interval of approximately 2 hr and a sustaining solution of the same composition was continued at a rate of 6–8 ml/min throughout the remainder of the study. At least three experimental clearance periods were obtained after volume expansion had been effected. In several patients, after completion of the latter periods, the saline infusion was continued and an edema-forming stimulus was induced. This consisted of the application of tourniquets to both thighs at subdiastolic pressures (1). After an equilibration period of 20–30 min, two additional clearance periods were obtained with the cuffs inflated.

Increase in GFR without volume expansion. We have found that the administration of bovine parathyroid hormone (PTH) increases GFR in most uremic patients. To examine the effects of an increase in GFR without volume expansion, the patterns of sodium excretion were studied after the intravenous administration of 250 U of PTH as a priming dose and the infusion of 1 U/min of PTH. Three control periods were obtained before PTH administration and three or more clearance periods were collected during the infusion of PTH.

The clearance of inulin was used to measure GFR. Corrections were made for inuloid blank in the plasma (as a concentration term) and for the excretion of inuloid blank in the urine (as an excretion rate term). The duration of individual clearance periods ranged from 12 to 40 min, depending upon the rate of urine flow. Indwelling catheters were employed for the volume expansion and PTH infusion studies, and rigorous aseptic technique was maintained in the manner described previously (2). No patients developed a urinary tract infection. (Urine cultures were obtained routinely at the end of these studies and on at least two occasions subsequent to the day of study.) When a catheter was used, each urine collection period was concluded with at least two bladder rinses with distilled water and one or more rinses with air. When voided urines were collected, the collection periods were prolonged and the patients either sat or stood during the brief interval of time required to collect the urine. Blood was collected at the midpoint of each clearance period by an indwelling venous catheter. Creatinine and urea clearances were performed on the same samples of plasma and urine used for inulin determinations. The mean value of creatinine plus urea clearances closely approximated the concurrent values for inulin clearance, thus serving as a check on the validity of the inulin clearance values (3).

Inulin was determined according to the method of Roe, Epstein, and Goldstein (4) and plasma and urine sodium concentrations were measured on a flame photometer (Instrumentation Laboratory Inc., Watertown, Mass.).

RESULTS

The results of sodium balance studies on eight patients maintained on both a 3.5 and 7.0 g salt diet are shown in Fig. 1. GFR for the group ranged from a maximum of 25 ml/min to a minimum of 2.6 ml/min. In each of these patients, external sodium balance was maintained on both levels of salt intake with reasonable accuracy.

The relationship between the fraction of filtered sodium excreted and the GFR over a range of GFRs from 2 to 120 ml/min is shown in Fig. 2. In the insert, two theoretical curves are presented

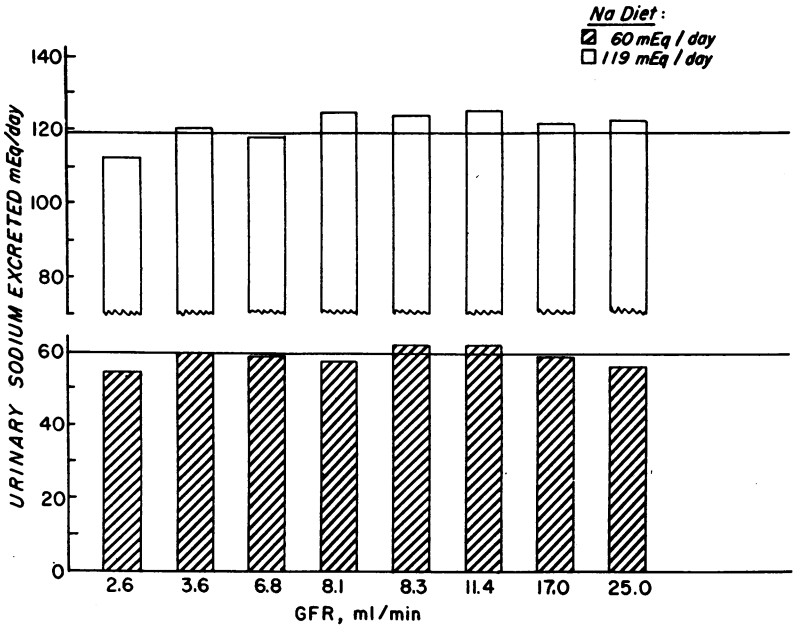

FIGURE 1 Sodium balance studies on 3.5 and 7.0 g salt diets. The horizontal lines represent sodium intake. The height of the vertical bars represents the mean of at least 2 24-hr sodium excretion rates. GFR, glomerular filtration rate.

to depict the patterns of sodium excretion that are required for the maintenance of external sodium balance on a constant intake of 3.5 and 7.0 g of salt, respectively, as the nephron population (and GFR) diminishes. The lower the GFR, the greater must be the fraction of sodium excreted. With both levels of salt intake, the relationship is such that for every 50% reduction in GFR, fractional excretion increases twofold. Moreover, at any given GFR, the lower the value for GFR the greater is the change in fractional sodium excretion associated with the increase in salt intake from 3.5 to 7.0 g/day. The experimental points derived in the present studies are shown in

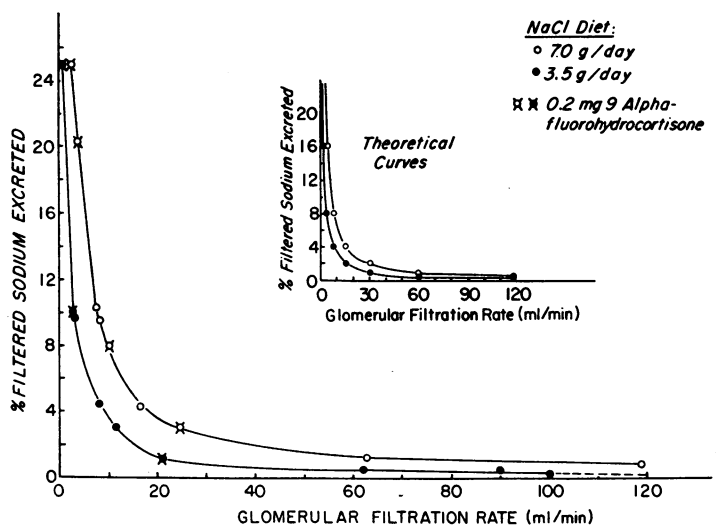

FIGURE 2 The relationship between steady-state GFR and the fraction of filtered sodium excreted on 3.5 and 7.0 g salt diets.

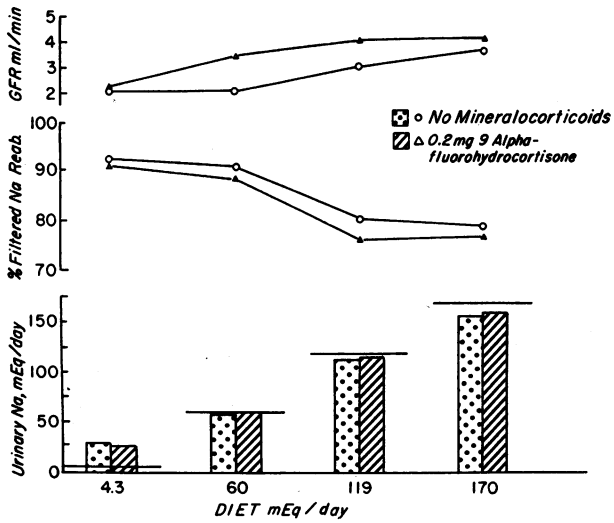

FIGURE 3 GFR, fractional sodium reabsorption, and external sodium balance with and without fluorohydrocortisone on varying salt intakes. The upper part of Fig. 3 represents data from clearance studies, the lower part balance measurements.

the two principal curves in Fig. 2. On both the 3.5 g and the 7.0 g salt diet, the curves transcribed closely resemble the theoretical ones. In approximately half of these studies, fluorohydrocortisone was administered daily; in the rest, no exogenous mineralocorticoid hormone was given. No difference is discernible between the two populations.

A more detailed examination of the influence of fluorohydrocortisone on sodium excretion in a patient with a markedly reduced GFR is shown

TABLE I

Effects of Extracellular Fluid Volume Expansion on the Filtered Load of Sodium and Sodium Excretion

Experiment	GFR	ΔGFR	FL*	U_{Na}	V	$U_{Na}V$‡	ΔFL	$\Delta U_{Na}V$	$\frac{\Delta U_{Na}V}{\Delta FL}$	Fractional reabsorption§	ΔFractional reabsorption
	ml/min	%	*μEq/min*	*μEq/ml*	*ml/min*	*μEq/min*	*μEq/nim*	*μEq/min*	%	%	
1 Control	25.9		3438	71.7	1.79	127				96.4	
Expansion	24.3	−6.18	3027	39.1	4.46	178	−411	+51		94.1	−2.3
2 Control	11.4		1500	62	2.03	124				91.7	
Expansion	9.47	−16.9	1222	50.5	2.41	128	−278	+4		89.5	−2.2
3 Control	7.11		925	55.8	2.37	132				85.7	
Expansion	7.36	+3.52	928	49.0	3.38	190	+3	+58		79.5	−6.2
4 Control	4.15		536	78.6	1.52	119				77.8	
Expansion	3.36	−19.0	417	60.9	2.53	153	−119	+34		63.3	−14.5
5 Control	3.35		423	72.2	1.47	117				72.5	
Expansion	3.64	+8.66	442	77.1	2.13	164	+19	+47	247	62.9	−9.6
6 Control	2.60		322	30.6	0.86	26.4				91.8	
Expansion	2.97	+14.2	347	40.8	1.98	79.8	+25	+53.4	214	77.0	−14.8
7 Control	3.85		510	54.2	1.06	57.7				88.7	
Expansion	5.04	+30.9	634	53.1	2.47	131	+124	+73.3	59.1	79.3	−9.4
8 Control	3.16		380	48	1.61	72.2				81.0	
Expansion	4.59	+47.2	535	59.1	2.54	150	+155	+77.8	50.2	72.0	−9.0
9 Control	2.90		355	49.7	1.69	82.5				77.0	
Expansion	4.82	+66.0	543	63.4	3.29	211	+188	+128	68.3	61.1	−15.9

* FL, filtered load of sodium (a Donnan factor of 0.95 was used in these calculations).

‡ $U_{Na}V$, sodium excretion rate.

§ Fractional reabsorption, the fraction of filtered sodium reabsorbed.

TABLE II

Effects of Increasing GFR (Secondary to PTH Administration) on the Filtered Load of Sodium and Sodium Excretion

Patient	GFR	ΔGFR	FL	U_{Na}	V	$U_{Na}V$	ΔFL	$\Delta U_{Na}V$	$\frac{\Delta U_{Na}V}{\Delta FL}$	Fractional reabsorption	ΔFractional reabsorption
	ml/min	%	*μEq/min*			*μEq/min*	*μEq/min*	*μEq/min*	%	%	
1 a Cont.*	3.21		444	72	1.15	84.2				81.1	
PTH‡	3.76	17.1	514	64	1.61	103	+70	+18.8	26.9	80.0	−1.1
b Cont.	3.05		319	77.4	1.28	85.8				78	
PTH	3.49	14.4	439	68.8	1.49	101	+48	+15.2	31.7	77.1	−0.9
c Cont.	3.47		492	73.3	1.34	98.5				80.0	
PTH	4.57	31.7	645	73.7	2.19	160.6	+153	+62.1	40.6	75.0	−5.0
2 a Cont.	16.7		2139	47.9	1.91	89.4				95.8	
PTH	19.1	14.4	2406	43.9	3.84	168.8	+267	+79.4	29.7	93.0	−2.8
b Cont.	14.4		1861	38.3	1.90	72.1				96.0	
PTH	16.0	10.4	2024	39.8	2.93	117.4	+163	+45.3	27.8	94.2	−1.8
c Cont.	13.6		1728	57.3	3.04	173.8				89.9	
PTH	16.5	21.3	2045	44.1	4.40	195.9	+317	+22.1	7.0	90.5	+0.6
3 a Cont.	3.02		399	65.5	1.80	118				70.4	
PTH	3.38	11.9	455	68.5	2.05	142	+56	+24	42.9	68.7	−1.7
b Cont.	2.87		375	85.5	1.50	125				66.7	
PTH	3.38	17.8	441	83.0	1.63	147	+66	+22	33.3	66.5	−0.2
c Cont.	2.48		328	42.1	0.88	30.7				90.6	
PTH	2.95	19.0	390	43.8	0.96	35.0	+62	+4.3	6.9	91.0	+0.4
d Cont.	2.33		310	42.3	0.73	30.8				90.0	
PTH	2.86	22.7	378	43.9	0.96	34.9	+68	+4.1	6.0	90.8	+0.8
4 a Cont.	12.0		1608	26.9	4.02	108				93.3	
PTH	13.7	14.2	1816	28.8	4.66	134	+208	+26	12.5	92.6	−0.7
b Cont.	9.69		1191	46.8	3.46	162				86.4	
PTH	11.6	19.4	1425	31.7	3.62	115	+234	−47	−20.1	91.9	+5.4
c Cont.	8.27		1017	39.3	2.68	105				89.7	
PTH	10.4	25.8	1256	35.0	4.04	141	+239	+36	15.1	88.8	−0.9
5 a Cont.	6.32		818	52.6	1.99	105				87.2	
PTH	7.95	25.7	1026	71.6	1.97	141	+208	+36	17.3	86.2	−1.0
b Cont.	5.49		754	52.2	2.11	99.6				86.8	
PTH	6.55	19.3	820	62.2	2.10	109	+66	+9.4	14.2	86.4	−0.1
6 Cont.	7.91		1025	73.5	1.88	141				86.3	
PTH	8.72	10.2	1113	74.2	2.03	151	+88	+10	11.4	86.5	+0.2
7 Cont.	3.30		410	57.5	1.70	97.9				76.1	
PTH	3.93	19.1	483	45.9	2.29	105	+73	+7.1	9.7	78.3	+2.2
8 Cont.	5.11		651	51.9	3.10	162				75.3	
PTH	7.81	53.0	997	56.7	4.77	269	+346	+107	31.0	73.0	−2.3
Mean		20.4					+152	+26.8	19.1		−0.54

* Cont., control periods; ‡ PTH, administration of parathyroid hormone; a, b, c, and d refer to separate studies in the same patient. In Patient 3 the first two studies were performed on a higher daily salt intake than the last two, thus the differences in control fractional reabsorption.

in Fig. 3. Studies were performed on four levels of salt intake (250 mg, 3.5 g, 7.0 g, and 10 g per day) with and without fluorohydrocortisone administration. Sodium balance was maintained both with and without mineralocorticoid administration on the 3.5 and 7.0 g salt diets. On the 250 mg salt diet, negative sodium balance ensued, and on the 10 g salt diet slight positive sodium balance ensued; but fluorohydrocortisone did not appear to influence the regulatory capacity. In clearance studies, GFR tended to be somewhat higher with fluorohydrocortisone and, thus, fractional sodium reabsorption was somewhat lower.

The effects of acute expansion of ECF volume in nine patients are shown in Table I. Fractional sodium reabsorption decreased in all nine patients, ranging from −2.2% to −15.9%. The mean decrement for the group was −9.3%. In general, the lower the steady-state GFR, the greater the decrease in fractional sodium reabsorption. GFR increased in six of the nine patients and decreased in three. In six of the studies, including the three patients in which GFR decreased, the increment in sodium excretion rate was quantitatively greater than the contemporaneous change in the filtered load of sodium. Sodium excretion rate increased in five of the six patients and remained essentially unchanged in one; but in the latter patient, filtered sodium decreased. In the three studies in which the increase in filtered load exceeded the increase in sodium excretion rate, the increment in excretion varied from 50.2 to 68.3% of the concurrent increment in filtered sodium. Fractional sodium reabsorption decreased substantially in each of these three patients.

The effects of increasing GFR without expanding ECF volume (i.e., by parathyroid hormone infusion) are depicted in Table II. 18 experiments were performed on 8 patients. In each study, GFR increased; for the group the range was from 10.2 to 53% with a mean of 20.4%. In contrast to the pattern presented in Table I, fractional sodium reabsorption changed very little in most studies; the changes also occurred in both directions. The mean change for the entire group was −0.54% and the range was −5.0 to +5.4%. The filtered load of sodium increased uniformly, and in each study the increment exceeded the concurrent in-

TABLE III

Effects of Extracellular Volume Expansion before and after PTH Infusion on Sodium Excretion

Period	Time	GFR	ΔGFR	V	U_{Na}	FL	ΔFL	$U_{Na}V$	$\Delta U_{Na}V$	$\frac{\Delta U_{Na}V}{\Delta FL}$	Fractional reabsorption
	min	*ml/min*	%	*ml/min*	*μEq/ml*	*μEq/min*	*μEq/min*	*μEq/min*	*μEq/min*	%	%
Inulin prime and sustain started at −84 min.											
1	0–22	3.42		1.76	70.5	439		124			71.8
2	22–38	3.49		1.56	75.2	438		117			73.3
3	38–50	3.13		1.54	70.8	393		109			72.3
Mean		3.35		1.61		423		117			72.5
2000 ml hypotonic saline infused from 51 to 202 min. Sustaining infusion delivered at 8 ml/min.											
4	202–222	3.57		2.04	76.0	438		155			64.6
5	222–239	3.74		2.21	75.1	458		166			63.8
6	239–255	3.61		2.13	80.2	429		170			60.4
Mean		3.64	+8.7	2.13	77.1	442	+19	164	+47	247	62.9
250 U PTH infused as a priming dose. 1 U/min delivered with hypotonic saline sustaining solution.											
7	303–318	4.66		2.87	80.1	571		230			59.7
8	318–343	4.33		2.95	69.7	535		205			61.7
9	343–362	4.37		2.71	76.4	558		207			62.9
Mean		4.45	+22.2	2.84	75.4	555	+113	214	+50	44.2	61.4

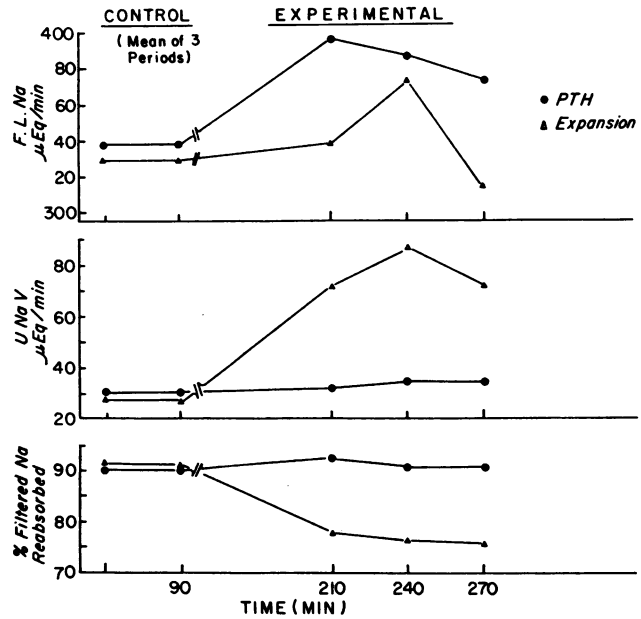

FIGURE 4 The comparative effects on the patterns of sodium excretion of extracellular fluid (ECF) volume expansion vs. an increase in GFR without volume expansion induced by parathyroid hormone administration. In the expansion study, urinary sodium concentrations averaged 30.6 mEq/liter during control periods and 40.8 mEq/liter during expansion. In the PTH study, the control and experimental values were 42.3 and 43.9 mEq/liter, respectively. Urinary volumes averaged 0.86 and 1.98 ml/min during control and expansion periods and 0.73 vs. 0.96 ml/min in control and PTH infusion periods, respectively.

crease in sodium excretion by a substantial degree. In one study, sodium excretion rate decreased; in the remaining 17 studies, it increased. The over-all increase in excretion averaged only 19.1% of the concurrent increase in filtered load with a range of −20.1 to +42.9%. Thus there was no overlap in values for $\Delta U_{Na}V/\Delta FL$ between the present studies and those presented in Table I.

Table III shows in detail the effects of superimposing an increase in GFR on preexisting ECF volume expansion. After three control periods, three clearance periods were obtained during volume expansion; then parathyroid hormone was administered while the rate of the sustaining solution used to maintain ECF expansion was maintained constant. ECF expansion was associated with an 8.7% increase in GFR and a decrease in fractional sodium reabsorption from 72.5 to 62.9%. The increase in sodium excretion rate was 247% of the increase in filtered sodium. Subsequent to the administration of PTH, GFR increased by 22.2% from the level achieved during the preceding expansion periods. Despite this change in GFR and filtered sodium, fractional sodium reabsorption decreased only from 62.9 to 61.4% and the increment in sodium excretion rate averaged 44.2% of the concurrent increment in filtered sodium.

Fig. 4 presents a comparison of the effects of increasing GFR by hypotonic expansion and by PTH infusion in separate studies on the same patient. The increase in filtered sodium was greater with PTH than with expansion; yet sodium excretion rate increased by over threefold during ECF expansion, whereas almost no change was observed in the absence of volume expansion. Finally, fractional reabsorption of sodium decreased from 91.8 to 77% with hypotonic expansion; but it did not change during PTH infusion. Similar results were obtained in two other patients in whom both experiments were performed.

Detailed protocols are presented in Table IV for two patients in whom blood pressure cuffs were inflated about both thighs at the conclusion of the third clearance period in the volume-expanded state. Before inflation of the cuffs in both patients, the increment in sodium excretion rate induced by the saline infusion could not be accounted for quantitatively by the change in filtered load. After inflation of the cuffs to pressures slightly under diastolic blood pressure, and with the continuation of hypotonic saline infusion, the effects of volume expansion were reversed in direction. Thus, in comparison with the values obtained during the expansion periods sodium excretion rate decreased, the change in the filtered load of sodium did not parallel the change in excretion, and fractional sodium reabsorption increased.

TABLE IV

Effects of Extracellular Fluid Volume Expansion and the Influence of a Superimposed Edema-Forming Stimulus on Sodium Excretion in Uremic Patients

Patient	Period	Time	GFR	F.F.	C_{PAH}	V	FL	$U_{Na}V$	Fractional reabsorption
		min	*ml/min*			*ml/min*	*μEq/min*	*μEq/min*	%
A									
Inulin prime and sustain (2 ml/min) started at −52 min.									
	1	0–12	23.8	0.25	96.2	1.43	3151	117	96.3
	2	12–26	27.9	0.25	109.6	2.07	3722	135	96.4
	3	26–43	25.9	0.26	98.4	1.87	3442	125	96.4
	Mean		25.9	0.25	100.4	1.79	3438	127	96.4
2000 ml of hypotonic saline infused from 44 to 141 min. Sustaining infusion delivered at 8 ml/min.									
	4	141–159	22.6	0.28	80.4	4.06	2893	174	94.0
	5	159–172	24.4	0.27	91.0	4.73	3040	173	94.3
	6	172–189	24.9	0.26	95.1	4.88	3147	185	94.1
	Mean		24.3	0.27	88.8	4.46	3027	178	94.1
Inflation of blood pressure cuffs about thighs at subdiastolic pressures at 190 min.									
	7	220–236	21.1	0.26	82.1	4.81	2680	134	95.0
	8	236–258	25.5	0.29	89.0	4.09	3198	143	95.5
B									
Inulin prime and sustain (2 ml/min) started at −98 min.									
	1	0–34	2.66	0.22	11.9	0.91	329	28.8	91.2
	2	34–64	2.69	0.22	11.9	0.89	335	26.4	92.1
	3	64–83	2.45	0.22	10.8	0.79	303	23.9	92.1
	Mean		2.60	0.22	11.5	0.86	322	26.4	91.8
1500 ml hypotonic saline infused from 84 to 179 min. Sustaining infusion delivered at 6 ml/min.									
	4	179–191	2.91	0.26	11.1	1.67	340	75.6	77.8
	5	191–203	3.31	0.25	13.4	2.13	387	91.0	76.5
	6	203–215	2.68	0.25	10.6	2.13	313	72.8	76.7
	Mean		2.97	0.25	11.7	1.98	347	79.8	77.0
Inflation of blood pressure cuffs about thighs at subdiastolic pressures at 216 min.									
	7	236–256	3.20	0.24	13.6	1.49	367	57.2	84.4
	8	256–276	2.55	0.22	11.7	1.20	298	37.4	87.4

DISCUSSION

The kidney must make essentially the same contribution to the preservation of sodium balance in chronic renal disease as in health. Thus, excretion must be correlated with the intake of sodium, rather than with the number of functioning nephrons. This requires a continuing change in the excretory profile of individual nephrons as their numbers diminish. If salt appetite and intake do not change substantially as the underlying disease advances, excretion of sodium/nephron must increase as the nephron population diminishes.

In the present study, some aspects of sodium excretion have been examined in patients with chronic renal disease. On two different levels of salt intake (3.5 and 7.0 g/day), external sodium balance was maintained in a group of patients encompassing a wide range of GFRs and, presumably, an equally wide range of severity of underlying disease. In accordance with theoretical

requirements for external balance, for every 50% reduction in steady-state GFR, the fraction of filtered sodium excreted was approximately doubled. Moreover, in individual patients, in the transition from 3.5 to the 7.0 g salt intake, the lower the GFR, the larger was the change in fractional sodium excretion. Similar data have recently been reported by Kleeman, Okun, and Heller (5).

The fact that fluctuations in sodium excretion/nephron must be very large at low GFR opens the possibility for differentiating between the contribution of tubular vs. glomerular factors in the modulation of sodium excretion in man. The basis for this statement is as follows: An increase in daily salt intake of 3.5 g requires an increase in sodium excretion of approximately 60 mEq/day or an average of 41 μEq/min. At a GFR of 120 ml/min, a change in GFR of only 1% would increase the delivery of sodium to the tubules by about four times this amount; it therefore is virtually impossible to distinguish a subtle change in GFR from an alteration in tubular reabsorption under these conditions. In contrast, at a GFR of 4 ml/min, a 1% change would increase the filtered load by less than 6 μEq/min; thus, if GFR changes determined the increased excretion, a much larger fractional change in GFR would be required. On the other hand, if tubular changes were responsible, the change in fractional excretion of sodium would be about 16 times as great, at a GFR of 4, as at a GFR of 120. With larger saline loads, the exaggerated swings in excretion/nephron required of the diseased kidney might enhance the ability to discriminate between tubular and glomerular factors.

The results of ECF volume expansion in patients with low filtration rates (Table I) suggest that changes in fractional sodium reabsorption, rather than GFR, played the key role in modulating excretion. In six of the nine studies, the changes in sodium excretion could not be accounted for quantitatively by concomitant changes in GFR; indeed, in three patients GFR decreased. Even in the three studies, in which filtered sodium increased more than sodium excretion, the increment in excretion ranged from 50 to 68% of the simultaneous increment in the filtered load. Thus, less than half of the increment in filtered sodium was reabsorbed. The composite data thus imply that hyperfiltration is not the major determinant of the decrease in fractional sodium reabsorption. However, to examine this question experimentally, the studies with PTH were performed (Table II). The results indicate that when GFR was increased without concomitant expansion of ECF volume, the increment in sodium excretion rate averaged only 19% of the increment in filtered sodium[1]; thus an average of 81% of the increased filtered load of sodium was reabsorbed. The changes in fractional sodium reabsorption in these patients generally were small, and in 6 of the 18 studies fractional reabsorption *increased*. These findings are in marked contrast to those observed in the patients subjected to ECF volume expansion. The study presented in Table III is of interest in terms of the differential effects between saline loading and hyperfiltration. In consequence of ECF volume expansion, GFR increased by 8.7%, whereas fractional sodium reabsorption decreased from 72.5 to 62.9%. ECF expansion was then maintained and an increase in GFR was superimposed by the infusion of PTH. GFR increased by an additional 22.2%; yet fractional sodium reabsorption stayed almost constant, decreasing from the previous level of 62.9% to an average of 61.4%. Thus net sodium reabsorption increased with the PTH-induced increment in GFR (and filtered load) despite the presence of volume expansion; but glomerulo-tubular balance for sodium remained essentially constant. The dissociation between the effects of a primary increase in GFR and an increase attendant upon saline loading is also depicted in Fig. 4. ECF expansion and PTH infusion were performed on separate days. Hyperfiltration was greater with PTH infusion; yet the latter produced relatively little effect on sodium excretion, whereas ECF expansion initiated a substantial reduction in fractional sodium reabsorption. Two other patients were studied during both volume expansion and PTH infusion and the results are included in Tables I and II.[2]

We believe that the foregoing data are consistent with the view that a factor (or factors)

[1] These results are similar to those recently reported by Lindheimer, Lalone, and Levinsky in dogs in which GFR was increased without expanding ECF volume (6).

[2] Data from three patients in whom both studies were performed are designated as Experiments 3, 4, and 6 in Table I, and as Patients 3, 7, and 8 in Table II.

other than changes in filtration rate and mineralocorticoid hormone activity participated in the modulation of sodium excretion in the uremic patients. Phenomenologically, the change in fractional sodium reabsorption after ECF volume expansion has the same charactertistics as those observed in normal animals receiving saline infusions (7) where at least one of the determining events presumably is a hormone (8). The sustained increase in sodium excretion rate/nephron observed in dogs subjected to a marked reduction in nephron population also appears to be mediated by the same factor(s) (9). Theoretically the changes in fractional sodium reabsorption associated with volume expansion in the present patients could be mediated by an increase in activity of a natriuretic hormone; alternatively it could relate to hemodynamic changes within the kidney (10). Finally, a combination of both events could be responsible. Although intuitively we would favor the change in activity of a hormone as being the most likely *modulator,* further observations are necessary to determine the relative importance of the various possible contributing factors.

ACKNOWLEDGMENT

This study was supported by U. S. Public Health Service Research grants AM-09976 and FR-36, General Clinical Research Centers Branch, Division of Research Facilities and Resources.

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