On the Adaptation in Sodium Excretion in Chronic Uremia

THE EFFECTS OF "PROPORTIONAL REDUCTION" OF SODIUM INTAKE

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ABSTRACT Renal mass and glomerular filtration rate (GFR) were reduced from normal to approximately 15% of normal in two groups of dogs. One group received a constant salt intake (CSI) throughout the study. The second group was subjected to "proportional reduction" of sodium intake (PRS), a dietary regimen which involved the reduction of sodium intake in exact proportion to the decrement in GFR. In the CSI group, absolute sodium excretion rate ($U_{Na}V$) remained essentially unchanged as GFR fell, while fractional sodium excretion (FE_{Na}) increased progressively from a mean control value of 0.3% to a final value of 4.4%. In the PRS group, $U_{Na}V$ decreased with each reduction in GFR and salt intake, and FE_{Na} remained constant throughout. In a second study, the fraction of serum that previously has been shown to possess natriuretic activity in studies of uremic patients was obtained from a group of uremic dogs on the CSI and from another group on the PRS regimen, and the effects of the fraction was measured on sodium excretion in rats. The serum fractions from the dogs on the CSI regimen produced a significant increase in both $U_{Na}V$ and FE_{Na} in the assay rats. The same serum fraction from the dogs on the PRS regimen failed to produce a significant increase in either $U_{Na}V$ or FE_{Na}.

The data are consistent with the view that (*a*) The increase in FE_{Na} in chronically uremic dogs is dictated by the requirements for external sodium balance and may be prevented by prospective manipulation of salt intake; (*b*) a natriuretic factor, previously shown to exist in the serum of patients with chronic uremia, is also demonstrable in the serum of uremic dogs; and (*c*) with the present bioassay system, the factor is not detectable in the serum fraction of uremic dogs in which the requirements for an increased natriuresis per nephron have been obviated.

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INTRODUCTION

The progressive rise in sodium excretion per nephron which accompanies the fall in glomerular filtration rate (GFR)[1] is a highly characteristic feature of advancing chronic renal disease (1, 2). This change in renal function is generally viewed as an adaptation, mediated by a biologic control system (3). The basis for the change presumably resides in the fact that, with a relatively constant intake of salt and a decreasing number of excretory units, an increase in sodium excretion per residual nephron is essential for the maintenance of salt balance. However, if the natriuresis per nephron is truly adaptive in nature, it should follow that, if the biologic need for the adaptation were to be obviated, fractional sodium excretion should remain constant, i.e. at the level existing before the onset of nephron destruction, even in the presence of very low levels of GFR.

To obviate the need for the adaptation would require only that sodium intake in the diet be diminished each time GFR falls and by the same percentage as the decrement in GFR. Under these circumstances, a progressive rise in fractional sodium excretion would be inappropriate and, rather than serving to protect the constancy of

[1] *Abbreviations used in this paper:* CSI, constant sodium intake; FE_{Na}, fractional sodium excretion rate; GFR, glomerular filtration rate; PRS, "proportional reduction" of sodium intake; $U_{Na}V$, absolute sodium excretion rate.

extracellular fluid volume, would lead to sodium depletion.

The present studies were undertaken to examine the effect of "proportional reduction" of sodium intake (PRS) in dogs subjected to experimental reduction of renal mass and GFR. Parallel studies were performed on dogs which were subjected to a comparable decrease in renal mass, but were maintained on a constant salt intake (CSI). Serial measurements of the patterns of sodium excretion were made in the two groups of dogs as renal function decreased. In addition, studies were also performed on the natriuretic activity of a low molecular weight fraction of serum from a group of uremic dogs maintained on the CSI regimen and from another group of uremic dogs maintained on the PRS regimen. The same bioassay procedure was employed as was used previously in demonstrating a natriuretic factor in the serum of chronically uremic patients (4).

If increased rates of sodium excretion per nephron in chronic uremia are due to a physiologic adaptation, fractional sodium excretion should differ markedly between the CSI and PRS groups of dogs as uremia evolves. Moreover, if the circulating natriuretic factor plays a role in mediating the natriuretic response, there should be a demonstratable difference in the bioassay results between two groups of dogs, equally uremic, one with a high, the other with a low rate of sodium excretion per nephron.

METHODS

Physiologic studies. The first portion of these studies was designed to measure the influence of different sodium intakes on GFR and fractional sodium excretion during the development of uremia in dogs. Experiments were performed on female mongrel dogs weighing 15–20 kg. A sodium-deficient diet (ICN Nutritional Biochemical Div., International Chemical and Nuclear Corp., Cleveland, Ohio) was prepared in a semiliquid form to which the appropriate amount of sodium was added as NaCl. The animals were trained and received the diet in two equal feedings daily through an orogastric tube. The twice daily intubation was tolerated without difficulty. In all dogs, base-line determinations of GFR (as measured by exogenous creatinine clearance), absolute sodium excretion rate ($U_{Na}V$), and fractional sodium excretion rate (FE_{Na}) were first made with both kidneys intact; thereafter, renal mass was reduced in two steps in order to decrease GFR from normal to a final value of approximately 10–15% of normal. In the first procedure, about 80% of the renal mass of one kidney was infarcted by ligating second- and third-order branches of the renal artery. In the second procedure, the contralateral kidney, which had not been altered in the initial procedure, was removed surgically. The experiments, which were performed while both kidneys were intact, are designated stage I; those performed after unilateral renal infarction are designated stage II; and those performed after contralateral nephrectomy are termed stage III.

The CSI group of animals was fed 120 meq sodium/day throughout the duration of the studies. In the PRS group of dogs, initial sodium intake (in stage I) was also 120 meq/day. However, after the stage I studies were completed, sodium intake was decreased in exact proportion to the decrement in GFR. To establish the appropriate degree of reduction of dietary salt, GFR was measured within 24 h of each surgical procedure. At each stage of study, the animals were maintained on their prescribed diet and salt intake for at least 1 wk before the experiments were performed.

The dogs were studied in the morning, unanesthetized, standing quietly in a supporting sling. A priming dose and sustaining infusion of 5% creatinine in a 2.5% dextrose vehicle were administered intravenously, the latter by constant infusion at 2.0 ml/min. Urine was collected through an inlying bladder cathether. A preliminary sample of urine was collected for 1 h with the dogs in the fasting state. Thereafter, half of the daily diet corresponding to the normal morning feeding and given at the same time (10 a.m.) was administered, and five 60-min clearance periods were obtained. The data presented in the text represent the average of these periods. A blood sample was collected at the midpoint of each urine collection period.

23 dogs were included in these studies. 13 were in the CSI group and 10 in the PRS group. All 23 dogs were studied in stages I and III. Six dogs from each group were also studied in stage II. In four of the dogs in the PRS group, serial studies were performed in stage III at approximately weekly intervals through the 37th day. In two additional PRS dogs, studies were performed 23 and 87 days after conversion to stage III.

Assay for natriuretic factor. In a second study, blood was obtained from 24 uremic, i.e. stage III dogs for assay of natriuretic factor. This group of dogs is not identical to that used in the physiologic studies, in that the assay studies were initiated after the physiologic studies were well in progress. Hence, additional dogs were prepared and studied in order to provide a comparable number of experiments in both phases of the study. However, the dietary regimens were identical in the two studies, and GFR and FE_{Na} were measured in all animals in close proximity to the time blood was obtained for the performance of each assay. 13 dogs were maintained on a constant salt intake of 120 meq/day, while 11 dogs were on the PRS regimen. Studies were performed only when the dogs had been on a given intake of salt for at least 1 wk. In some animals in both groups, two or more studies were performed. Three dogs in the CSI group had studies performed 7–13 days after the initial study. Four dogs in the PRS group had studies performed after a 43-day interval, and three of these dogs had studies repeated 61 days after the initial study.

To obtain the serum fraction for assay, 40–50 ml of blood was drawn through the external jugular vein before the administration of the morning feeding. The serum was subjected to gel filtration through Sephadex G-25 at 4°C with the use of a 10 mM ammonium acetate buffer of pH 6.8. The same elution fraction, which previously was found to possess natriuretic activity in the serum of patients with chronic uremia, was employed in these studies (5). A 1.0-ml aliquot of the serum fraction, which corresponds to 10 ml of original serum, was infused intravenously into a rat at a rate of 100 μl/min. The details of the preparative procedures and of the bioassay technique employed in the rat have been described previously (4–6). The fractions were coded, and the investigators performing the assays had no knowledge of the nature of the samples being tested.

GFR was measured in the dogs by the clearance of exogenous creatinine and in the bioassay rats by the clearance of ^{14}C inulin. Creatinine was determined by the method of Bonsnes and Taussky (7) using an auto-analyzer (model AA II, Technicon Instruments Corp., Tarrytown, N. Y.). Urea was measured by the method of Marsh, Fingerhut, and Miller (8). Radioactive inulin was counted in a liquid scintillation spectrometer (model 3330, Packard Instrument Co., Inc., Downers Grove, Ill.). Sodium was measured by using a flame photometer (model 143, Instrumentation Laboratories, Inc., Lexington, Mass.). Statistical analyses were performed by using Student's *t* test with significance being reported as the *2P* value.

RESULTS

Physiologic studies. In Table I, data are shown for GFR, $U_{Na}V$, and FE_{Na} in stages I, II, and III for both the dogs in the CSI group and those in the PRS group. In stage I, with both groups receiving a sodium intake of 120 meq/day, there were no significant differences in GFR, $U_{Na}V$, or FE_{Na} between the two groups.

In stage II, where values were compared to the stage I values for the same 12 dogs (6 in each group), GFR was decreased by 31.3% in the CSI group and by 36.2% in the PRS group. $U_{Na}V$ was slightly increased in the CSI group and slightly decreased in the PRS group; however, neither of the differences was statistically significant. FE_{Na} was significantly increased in the CSI dogs (from 0.27 to 0.74%; $P < 0.05$), while no significant change occurred in the PRS animals (from 0.27 to 0.42%).

In stage III, in the CSI group, GFR averaged 9.7 ml/min in comparison to the mean stage I value of 66.9 ml/min. The mean value for $U_{Na}V$ was 44.5±5.6 μeq/min in stage III vs. 31.2±8.3 μeq/min in stage I. Thus, despite a decrease in GFR of 85.5%, $U_{Na}V$ on CSI was undiminished. The basis for this is to be found in the increase in FE_{Na} from the stage I value of 0.30% to the mean value in stage III of 4.5% ($P < 0.001$).

In the PRS group, the mean value for GFR in stage III was 10.9 ml/min, a decrease from stage I of 86.9%. The values for GFR in stage III in the CSI and PRS

TABLE I

GFR and Sodium Excretion Rates in the CSI and PRS Groups of Dogs

Dog no.	Stage I			Stage II			Stage III		
	GFR	$U_{Na}V$	FE_{Na}	GFR	$U_{Na}V$	FE_{Na}	GFR	$U_{Na}V$	FE_{Na}
	ml/min	*μeq/min*	%	*ml/min*	*μeq/min*	%	*ml/min*	*μeq/min*	%
CSI group									
1	104.8	47.1	0.29	73.3	26.3	0.27	8.0	67.3	6.47
2	88.2	65.3	0.52	69.9	103.5	1.08	15.1	65.6	3.22
3	66.2	65.4	0.45	53.6	42.4	0.58	7.2	46.5	4.87
4	65.4	3.5	0.04	51.6	58.1	0.82	2.3	39.6	15.85
5	71.8	22.7	0.22	49.0	22.1	0.37	17.7	68.1	2.95
6	77.1	12.5	0.11	29.1	46.1	1.23	9.0	45.9	3.66
7	59.6	8.0	0.09				16.8	40.1	1.85
8	42.8	0.4	0.01				5.5	22.4	2.92
9	57.8	88.1	1.09				3.3	12.1	2.67
10	69.9	52.6	0.53				5.8	31.2	3.84
11	45.0	1.3	0.02				6.9	14.1	1.43
12	64.7	1.3	0.02				7.6	61.5	5.62
13	55.5	36.8	0.45				13.1	63.9	3.60
Mean±SE	66.9±4.6	31.2±8.3	0.30±0.09	54.4±6.5	49.8±12.0	0.74±0.16	9.7±1.4	44.5±5.6	4.53±1.02
PRS group									
1	118.2	97.8	0.55	61.3	36.4	0.45	8.9	1.6	0.14
2	80.8	47.3	0.40	61.4	32.4	0.38	8.4	2.2	0.19
3	89.3	5.9	0.05	63.7	31.8	0.36	7.5	3.4	0.33
4	92.5	9.3	0.07	59.2	19.5	0.22	13.4	6.7	0.39
5	60.8	2.4	0.03	34.7	33.4	0.70	10.6	6.6	0.47
6	65.4	43.7	0.49	41.9	24.9	0.42	7.0	4.7	0.52
7	58.5	28.0	0.35				9.8	32.3	2.39
8	63.3	14.2	0.16				17.4	31.4	1.29
9	88.2	65.3	0.52				12.1	3.0	0.17
10	112.3	19.2	0.43				13.8	6.5	0.36
Mean±SE	82.9±6.7	33.3±9.6	0.31±0.07	53.9±5.0	29.7±2.6	0.42±0.06	10.9±1.0	9.8±3.7	0.63±0.22
Difference CSI vs. PRS *P*	NS	NS	NS	NS	NS	<0.05	NS	<0.001	<0.005

Dogs in the CSI Group received 120 meq sodium daily in stages I, II, and III.
Dogs in the PRS Group also received 120 meq sodium daily in stage I. The dietary intake of sodium was then reduced in exact proportion to the decrement in GFR in stages II and III.
GFR, $U_{Na}V$ and FE_{Na} were determined after the animals had been fed half of their daily salt allotment.
Values are the average of five 60-min clearance periods (see Methods).

TABLE II

Clearance Data and Blood Urea Nitrogen on Dogs Whose Serum Fractions Were Used in the Bioassay of Natriuretic Factor

	GFR	$U_{Na}V$	FE_{Na}	BUN
	ml/min	*μeq/min*	%	*mg/100 ml*
CSI Group, n = 16 Mean±SE	9.0±1.0	48.7±6.7	3.68±0.53	47.0±5.8
PRS Group, n = 18 Mean±SE	12.0±0.9	6.1±0.7	0.39±0.05	55.1±5.7
$2P$	<0.05	<0.001	<0.001	NS

Values for GFR, $U_{Na}V$, and FE_{Na} represent the mean of the average of five 60-min clearance periods.

groups are not significantly different. There also was no significant difference for blood urea nitrogen in the two groups (58.3±6.5, CSI vs. 64.0±6.6 mg/100 ml, PRS). $U_{Na}V$, on the other hand, averaged 9.8 μeq/min in the PRS group, compared to 44.5 μeq/min in the CSI group ($P < 0.001$). FE_{Na} averaged 0.63% in the PRS group. This value is not significantly different from the stage I value for the same dogs, but it is significantly different from the stage III value for the CSI group ($P < 0.005$).

Serial studies were performed on four of the stage III PRS dogs at approximately weekly intervals for 5 wk. GFR and FE_{Na} averaged 9.6 ml/min and 0.26%, respectively, at 1 wk and 10.4 ml/min and 0.10% at 5 wk. In two additional dogs studied 23 and 87 days after nephrectomy, GFR was unchanged and FE_{Na} remained appropriately low. Thus, these dogs were able to maintain external balance on a low intake of sodium in the face of chronic renal failure for long periods of time.

Assay for natriuretic factor. The levels of renal function and patterns of salt excretion for the stage III CSI and PRS dogs, the serum fractions of which were bioassayed for natriuretic activity, are shown in Table II. The mean GFR for the dogs in the CSI group was 9.0±1.0 vs. 12.0±0.9 ml/min in the PRS group. The mean values for $U_{Na}V$ (CSI vs. PRS) for the two groups were 48.7 vs. 6.1 μeq/min and for FE_{Na}, 3.68 vs. 0.39%. Both of the differences are statistically significant. The mean blood urea nitrogen values for the CSI group (47.0 mg/100 ml), and for the PRS group (55.1 mg/100 ml) were not significantly different.

Data on the assay rats are detailed in Table III. The base-line levels (before administration of the serum fractions) for GFR, $U_{Na}V$, and FE_{Na} for the two groups of rats did not differ significantly. In both groups of rats the change in GFR after infusion of the fraction was small and not statistically significant. After administration of the fraction from the CSI group, there was a mean increase in $U_{Na}V$ of 1.28 μeq/min and an increase in FE_{Na} of 1.42%. Both of these changes are statistically significant. With the fractions from the PRS group, $U_{Na}V$ changed by + 0.24 μeq/min and FE_{Na} by +0.13%. Neither of these changes is significantly different from zero. In comparing the changes for $U_{Na}V$ and FE_{Na} between the two groups, significant differences exist for both $U_{Na}V$ ($P = 0.02$) and FE_{Na} ($P < 0.02$).

DISCUSSION

The ability of patients and experimental animals to maintain external sodium balance as GFR falls in chronic renal disease without the necessity of imposing salt restriction suggests that the biologic control system which regulates sodium excretion in health continues to operate accurately in uremia. For this to occur requires that the intake of salt (or some derivative thereof) be detected and the appropriate information be relayed to the surviving nephrons. Moreover, the response per nephron (as expressed by FE_{Na}) to a given stimulus, i.e. the entry of a given amount of sodium into the extracellular fluid, must multiply as GFR falls. Theoretically, therefore, for the system to continue to oscillate about a normal or constant extracellular fluid volume, the sensitivity of the control system must increase as the nephron population diminishes. However, if the increased natriuresis per nephron in chronic renal disease is truly adaptive and is mediated by a control system that serves to regulate the constancy of extracellular fluid volume, fractional sodium excretion should not increase as GFR falls if the ratio between sodium intake and GFR remains constant. This condition can be met in the experimental animals by decreasing renal mass (and thus GFR) and simultaneously decreasing the intake of sodium in exact proportion to the fall in GFR. In previous studies, the use of proportional reduction of phosphorus intake was shown to prevent the adaptive increase in phosphaturia per nephron that regularly occurs in uremic dogs when phosphate intake is maintained constant (9).

TABLE III

Effects of Serum Fractions from Uremic Dogs on GFR and Sodium Excretion in Rats

CSI group							PRS group						
	Control periods			Experimental periods				Control periods			Experimental periods		
Dog study	GFR	$U_{Na}V$	FE_{Na}	ΔGFR	$\Delta U_{Na}V$	ΔFE_{Na}	Dog study	GFR	$U_{Na}V$	FE_{Na}	ΔGFR	$\Delta U_{Na}V$	ΔFE_{Na}
	ml/min	*μeq/min*	%	*ml/min*	*μeq/min*	%		*ml/min*	*μeq/min*	%	*ml/min*	*μeq/min*	%
1	0.93	6.75	5.06	0.00	+1.97	+1.05	1*a*	0.43	1.98	3.63	+0.09	−0.06	−0.37
2	1.12	8.74	5.89	−0.12	−0.08	+0.65	*b*	0.26	1.69	4.78	−0.05	+0.43	+1.69
3	0.67	1.25	1.45	+0.18	+1.07	+1.46	*c*	1.05	6.20	4.83	−0.08	−1.98	−1.38
4*a*	0.71	5.16	5.49	+0.04	+1.35	+1.02	2*a*	0.83	3.10	2.70	−0.01	+0.17	+0.15
b	0.47	7.90	13.22	+0.08	+1.87	+0.77	*b*	0.34	0.89	1.65	+0.01	+0.54	+0.94
5	0.51	4.40	6.47	+0.38	+1.43	−1.53	3*a*	0.78	0.67	0.67	−0.02	+0.29	+0.24
6	0.80	5.92	5.23	−0.01	+1.91	+1.86	*b*	0.26	3.96	11.05	−0.01	−0.74	−1.40
7*a*	0.67	4.13	4.72	+0.03	+4.20	+4.33	*c*	0.91	7.45	6.09	+0.14	+3.41	+1.42
b	0.69	8.42	8.92	−0.04	+0.81	+1.02	4*a*	0.63	2.10	2.70	−0.01	−0.33	−0.41
8	0.81	5.37	5.15	−0.08	−1.33	−0.88	*b*	0.85	5.80	4.90	+0.07	+1.59	+0.87
9	0.46	4.65	7.44	+0.01	+1.14	+1.66	*c*	0.99	4.34	2.92	−0.16	−1.09	−0.36
10	0.54	5.41	7.53	−0.07	+0.19	+1.59	5	1.17	7.40	5.06	+0.07	+1.31	+0.24
11*a*	0.64	7.42	8.86	−0.08	+0.53	+1.44	6	0.51	4.67	7.05	−0.02	+0.09	−0.03
b	0.36	4.16	8.93	−0.04	+1.96	+5.84	7	0.96	5.61	4.62	−0.04	−0.89	−0.58
12	0.88	2.31	2.12	+0.15	+2.40	+1.40	8	0.58	5.26	5.70	−0.04	−0.29	−0.10
13	1.11	4.40	2.19	−0.06	+1.07	+1.00	9	0.46	5.20	9.12	−0.04	+1.88	+2.35
							10	1.05	7.46	5.57	+0.02	+0.79	+0.55
							11	1.27	8.47	5.12	+0.14	−0.77	−0.90
Mean	0.71	5.39	6.16	+0.02	+1.28	+1.42		0.74	4.57	4.90	0.00	+0.24	+0.13
±SE	±0.05	±0.52	±0.75	±0.03	±0.30	±0.43		±0.07	±0.57	±0.59	±0.02	±0.30	±0.24
P				NS	<0.001	<0.005		—	—	—	NS	NS	NS

The mean values for GFR, $U_{Na}V$, and FE_{Na} obtained during six consecutive 10-min clearance periods after infusion of the fractions were compared with the mean values obtained during the last two control clearance periods before the infusion. The mean values under experimental periods thus represent the differences in GFR, $U_{Na}V$, and FE_{Na} between the mean experimental and the control values (5).
Dog study indicates those animals in which two or more studies were performed (*a*, *b*, *c*).

The present data demonstrate that proportional reduction of sodium intake did indeed obviate the natriuresis per nephron that occurred in a characteristic fashion in dogs which were maintained on a constant intake of salt as renal insufficiency evolved. Thus, fractional excretion of sodium remained unchanged as GFR was diminished from a mean value of 82.9 to 10.9 ml/min in the PRS group, while, with a comparable fall in GFR, FE_{Na} rose from 0.30 to 4.5% in the constant salt intake group. Clinically, the animals subjected to PRS showed neither evidence of volume depletion nor any other adverse effects from the progressive reduction of salt intake.

These experiments also have bearing on the nature of the efferent limb of the control system governing sodium excretion. To date, the factors that account for the rising natriuresis per nephron in chronic uremia have not been elucidated fully.

In the present studies, comparison may be made between two groups of dogs with an equal reduction in renal mass and in GFR, which were receiving the same basic diet, were maintained under identical circumstances, and had the same degree of urea retention. Fractional excretion of sodium, however, was substantially greater in one group than in the other. These dogs thus offer an opportunity to determine whether the appearance in the serum of the circulating inhibitor of sodium transport, previously observed in chronically uremic patients, bears a relationship to the concurrent requirements for sodium excretion per nephron. In the group maintained on a constant salt intake and excreting an average of over 3.5% of the filtered sodium, the serum fractions produced a significant increase in both $U_{Na}V$ and FE_{Na} in the bioassay rats. The degree of natriuresis induced in the rats was closely comparable to that observed during use of the serum fraction from chronically uremic patients (5). In the PRS group with a mean FE_{Na} of 0.4%, the same gel filtration fraction of serum produced no significant increase in either $U_{Na}V$ or FE_{Na}, and the effects were similar to those produced by equivalent serum fractions from subjects with normal renal function (5).

We believe that the cumulative data support the view that the acquired natriuresis per nephron observed in the CSI group of uremic dogs was adaptive in nature rather than an obligatory concomitant of the uremic state. We also believe that the data are consistent with the view that the circulating natriuretic factor may have played a role in mediating the increase in fractional sodium excretion.

The availability of stable uremic dogs excreting less

than 0.5% of their filtered sodium (and as little as 0.1%) offers the opportunity to examine the adaptive changes in the excretion of a number of other solutes, the transport of which is coupled, directly or indirectly, to that of sodium.

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REFERENCES

1. Slatopolsky, E., I. O. Elkan, C. Weerts, and N. S. Bricker. 1968. Studies on the characteristics of the control system governing sodium excretion in uremic man. *J. Clin. Invest.* **47**: 521.
2. Schultze, R. G., H. S. Shapiro, and N. S. Bricker. 1969. Studies on the control of sodium excretion in experimental uremia. *J. Clin. Invest.* **48**: 869.
3. Bricker, N. S., S. Klahr, and H. Lubowitz. 1972. The kidney in chronic renal disease. *In* Clinical Disorders of Fluid and Electrolyte Metabolism. M. Maxwell and C. Kleeman, editors. McGraw-Hill Book Co., New York. 697.
4. Bourgoignie, J., S. Klahr, and N. S. Bricker. 1971. Inhibition of transepithelial sodium transport in the frog skin by a low molecular weight fraction of uremic serum. *J. Clin. Invest.* **50**: 303.
5. Bourgoignie, J. J., K. H. Hwang, C. Espinel, S. Klahr, and N. S. Bricker. 1972. A natriuretic factor in the serum of patients with chronic uremia. *J. Clin. Invest.* **51**: 1514.
6. Bourgoignie, J. J., Hwang, K. H., Ipakchi, E., and Bricker, N. S. 1974. The presence of a natriuretic factor in urine of patients with chronic uremia. The absence of the factor in nephrotic uremic patients. *J. Clin. Invest.* **53**: 1559.
7. Bonsnes, R. W. and H. H. Taussky. 1945. On the colorimetric determination of creatinine by the Jaffe reaction. *J. Biol. Chem.* **158**: 581.
8. Marsh, W. H., B. Fingerhut, and H. Miller. 1965. Automated and manual direct methods for the determination of blood urea. *Clin. Chem.* **11**: 624.
9. Slatopolsky, E., S. Caglar, L. Gradowska, J. Canterbury, E. Reiss, and N. S. Bricker. 1972. On the prevention of secondary hyperparathyroidism in experimental chronic renal disease using "proportional reduction" of dietary phosphorous intake. *Kidney Int.* **2**: 147.