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Influence of aldosterone on sodium, water and potassium metabolism in chronic renal disease

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Influence of aldosterone on sodium, water and potassium metabolism in chronic renal disease. To evaluate the physiological importance of aldosterone in chronic renal disease, 11 studies were performed in nine patients with renal impairment of varying etiology and severity during periods of normal and low sodium intake. Decreased sodium excretion during sodium restriction was accompanied by increased aldosterone excretion and this anti-natriuretic effect could be reversed by the administration of spironolactone. Constancy of urinary potassium excretion occurred during the period of sodium restriction and may have been related to a combination of diminished distal sodium delivery and increased aldosterone activity. Sodium restriction was also associated with a diminution in renal concentrating capacity and an improvement in renal diluting capacity. Only the improvement in renal diluting capacity, as judged by the minimal urinary osmolality achieved during an acute water load, could be reversed by the administration of spironolactone. These results thus suggest that aldosterone is of physiological importance to the control of urinary sodium, potassium and water excretion in patients with chronic renal disease.

Influence de l'aldosterone sur le metabolisme du sodium, de l'eau et du potassium dans l'insuffisance renale chronique. Pour juger de l'importance physiologique de l'aldostérone dans l'insuffisance rénale chronique, onze expériences ont été chez pendant des périodes de régime normal ou pauvre en sodium, sur neuf malades atteints d'insuffisance d'étiologies et de gravité variable. Pendant les périodes de restriction sodée, la diminution de l'excrétion du sodium était associée avec une excrétion accrue d'aldostérone. Cet effet antinatriurétique pouvait être annulé par l'administration de spironolactone. En période de restriction sodée, l'excrétion du potassium demeura constante, peut-être sous l'influence combinée d'un apport sodé moindre au niveau du tube distal et d'une activité plus grande de l'aldostérone. La restriction sodée s'accompagnait également d'une capacité moindre du rein à concentrer l'urine et d'une meilleure capacité de dilution. Seule l'amélioration de la capacité rénale de dilution, jugée par l'osmolalité urinaire minimale atteinte après surcharge hydrique, pouvait être annulée par l'administration de spironolactone. Ces résultats suggèrent donc que l'aldostérone joue un rôle physiologique important dans le contrôle de l'élimination urinaire du sodium, du potassium et de l'eau chez les malades atteints d'insuffisance renale chronique.

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The control of sodium excretion in the presence of normal renal function has been clearly demonstrated to be dependent on factors other than glomerular filtration rate and aldosterone activity [1–4]. Recent studies have demonstrated that a "third factor" may be involved in the regulation of sodium excretion in experimental uremia [5] and in patients with chronic renal failure [6, 7]. Moreover, the physiological role of such a "third factor" may be more important in chronic renal disease since, in contrast to normal subjects, it is possible that aldosterone may not be involved in the adjustments in sodium excretion in patients with chronic renal disease. This possibility is not unlikely since patients with advanced chronic renal disease who are receiving a normal sodium intake have been reported to have increased aldosterone secretory rates [8, 9] and thus may have persistently high endogenous levels of aldosterone. In the presence of already increased aldosterone activity, sodium restriction may not be associated with any significant alternation in either the level of aldosterone activity or the renal response to aldosterone. Some evidence for such a circumstance has been provided by the studies of Slatopolsky et al [6] in which the renal response to alterations in sodium intake in patients with severe chronic renal disease was found to be unaltered by the prior administration of supraphysiological levels of exogenous mineralocorticoid [6].

Although these results clearly implicate factors other than aldosterone in the regulation of sodium excretion by patients with chronic renal disease [6], they do not exclude an additional contributory role of aldosterone.

The present investigation was therefore undertaken to examine whether aldosterone is involved in the renal response to alterations in dietary sodium intake in patients with chronic renal failure. The results suggest that alterations in aldosterone activity do indeed contribute to the renal response to sodium restriction in patients with chronic renal disease, not only with respect to sodium excretion, but also with regards to the renal excretion of potassium and water.

Methods

Eleven studies were performed in nine patients with chronic renal disease. None of the patients had clinical evidence of uremia, edema, congestive heart failure, urinary tract obstruction or urinary tract infection. Each study consisted of a period on a normal sodium intake (2 mEq/kg/day) followed by a period on a low sodium intake (10 to 21 mEq/day). Each patient received the same basic diet and fluid intake (30 ml/kg) during periods of normal and low sodium intake. The patients ingested all of the food and fluid offered them throughout the study. A solution of sodium chloride was added to the basic diet during periods of normal sodium intake and was omitted during periods of low sodium intake. The dietary protein intake averaged 0.75 g/kg/day and the caloric intake ranged from 30 to 45 calories/kg/day, depending on the amount necessary to maintain a constant body weight in each individual patient during the period of normal sodium intake. The periods of normal sodium intake ranged from 7 to 15 days and the periods of low sodium intake ranged from 8 to 25 days. Sodium restriction was instituted when a constant body weight had been noted for at least three consecutive days, and terminated when the urinary sodium concentration had diminished to a low level that was constant for at least three days or when the serum sodium concentration approached 120 mEq/liter. Adverse clinical symptomatology was not observed during any of the studies.

Aldosterone excretion rates. After at least seven days on a normal sodium intake, three consecutive 24 hour urine collections were obtained for determination of aldosterone excretion rates. Three additional 24 hour urine collections were obtained consecutively at the end of each period of sodium restriction for the same determination. The acid-released conjugate of aldosterone was measured using the double isotope method of Kliman and Petersen [10]. The determinations were done by the Biomedical Assay Laboratory, Worchester, Mass., without knowledge of the sodium intake of the patients.

Glomerular filtration rate and volume studies. Endogenous creatinine clearance (C_{cr}) was used as an index of glomerular filtration rate (GFR) in those patients whose C_{cr} was greater than 10 ml/min. The mean of the C_{cr} and urea clearance was used as an index of GFR when the C_{cr} was less than 10 ml/min. Radioactive ^{131}I-tagged albumin, ^{35}S-sulfate and tritiated water were used to measure plasma volume, extracellular fluid (ECF) volume and total body water, respectively, during periods of normal and low sodium intake.

Sodium and potassium balances. Sodium and potassium balances were undertaken during ten of eleven studies with analyses of both urine and stool. Twelve hour urine volumes were collected from 7:30 AM to 7:30 PM and from 7:30 PM to 7:30 AM. Stool collections were divided into three day periods. A nitric-perchloric acid homogenate of stools was analyzed for sodium and potassium content. Blood specimens were obtained every other day. The blood and urine specimens were analyzed for sodium, chloride, potassium, urea, creatinine and osmolality. Sodium, potassium, urea, and creatinine were measured on the Technicon Autoanalyzer, and chloride was measured using an automatic Cotlove titrator. Urine and plasma osmolalities were measured cryoscopically on an Advanced osmometer. Osmolar clearance (C_{Osm}) was calculated by the formula: C_{Osm} = urine osmolality (U_{Osm})/plasma osmolality (P_{Osm}) × urine flow (V). Free water clearance (C_{H_2O}) and free water reabsorption (T^cH_2O) were calculated respectively as $C_{H_2O} = V - C_{Osm}$ and $T^cH_2O = C_{Osm} - V$. Clearances of creatinine and urea were calculated by standard methods.

Dilution and concentration tests. Standard dilution and concentration tests were performed at the end of both the normal and low sodium intake periods in the following manner: on the morning of the dilution tests, the patients emptied their bladders and then ingested an oral water load (20 ml/kg) over the next 30 minutes. Four one-hour urine collections were then obtained sequentially and blood specimens were drawn at the midpoint of each urine collection period. Hourly urine volumes were replaced with the oral administration of an equivalent volume of water. Following completion of the dilution test, fluid was restricted for the remainder of the day so that the total

24 hour intake did not exceed 30 ml/kg. At 9:00 PM on the same evening, fluid was completely withdrawn and five units of pitressin tannate in oil, shaken to a fine emulsion, were injected intramuscularly. At 7:30 AM the patients emptied their bladders, three or four one-hour urine collections were obtained consecutively, and blood specimens were drawn at the midpoint of each urine collection period. The patients were then placed on a low sodium intake until the minimal urinary sodium concentration was achieved; the urinary dilution and concentration tests were then repeated at that time.

In two studies the period of normal sodium intake was continued after completion of the concentration tests, and the patients were treated with 9-α-fluorohydrocortisone (1.0 mg) orally every six hours for five days. In a third study desoxycorticosterone acetate (10 mg) was administered intramuscularly for five days. On the fourth and fifth day of mineralocorticoid administration, the dilution and concentration tests were repeated in the same manner as described above. Dietary sodium restriction was then instituted and the concentration and dilution tests were repeated when the minimal urinary sodium concentration was achieved. Spironolactone (75 mg) was then administered orally every six hours for eight days and the dilution and concentration tests were repeated on the seventh and eighth day of its administration. In these same three patients, formation of T^cH_2O was examined after the performance of the concentration tests on both normal and low sodium intakes. These studies were performed during the infusion of 10% mannitol in sodium chloride (45 mEq/liter) at 10 ml/min for $1^1/_2$ to 2 hours. Aqueous vasopressin was also administered (50 mU/kg/hr).

Results

Effect of prolonged sodium restriction on urinary aldosterone excretion in chronic renal disease (Fig. 1). Three consecutive measurements of daily aldosterone excretion were obtained in nine patients after receiving a normal sodium intake for at least one week; similar measurements were then obtained in the same patient on a low sodium intake after a minimal urinary sodium concentration had been achieved (range: 8 to 25 days). The mean values for the three urinary aldosterone excretion rates in each patient on a normal and low sodium diet are shown in Fig. 1. The mean value observed on a normal sodium diet was 5.9± SEM 1 μg/24 h, and it increased after the period of prolonged sodium deprivation to 28.9 ± SEM 8.4 μg/24 hr. Although some values were within the range of normal after prolonged sodium deprivation, all of these values were increased when compared with the observed excretion rate in the same patient during the period of normal sodium intake. Arterial blood pressure was not significantly different during periods of normal and low sodium intake in any patient.

Effect of prolonged sodium restriction on glomerular filtration rate, blood urea nitrogen, body weight, total body water, extracellular fluid and plasma volume (Tables 1 and 2). In ten of the eleven studies in nine patients, prolonged dietary sodium restriction was associated with a diminution in GFR. The mean GFR

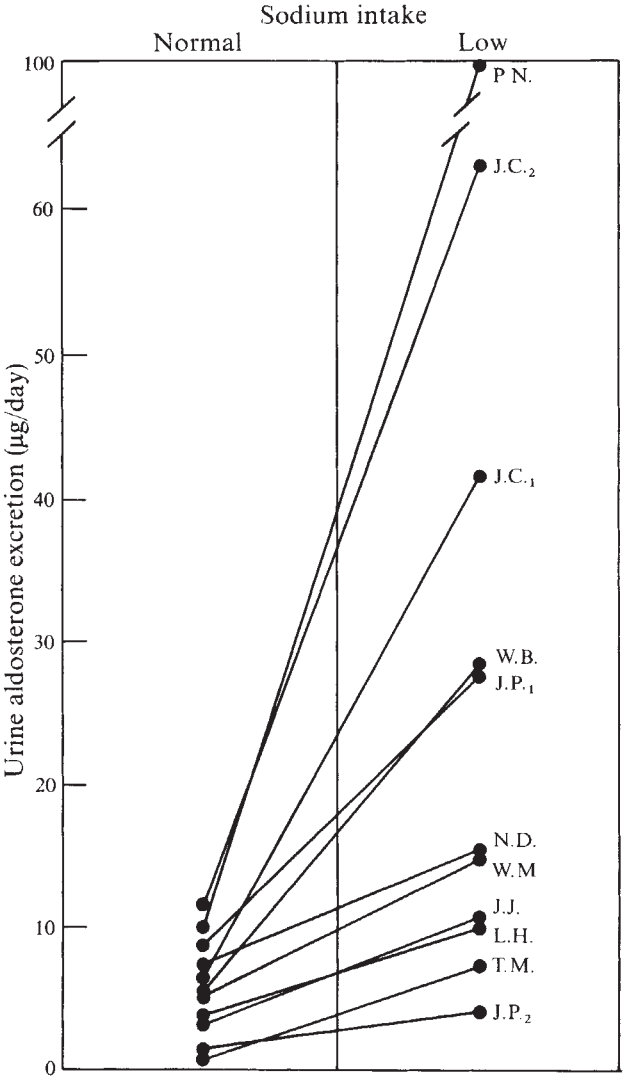

Fig. 1. *Effect of prolonged sodium restriction on aldosterone excretion rate.* Aldosterone excretion rates were not increased in any of the studies during the normal sodium intake but increased in each patient during sodium restriction.

Table 1. Summary of patients with chronic renal disease on normal and low sodium intake

Patient	Age/Sex	Diagnosis[a]	GFR[b] *ml/min*		BUN *mg/100 ml*	
			normal sodium	low sodium	normal sodium	low sodium
W. M.	37/M	Chronic glomerulonephritis	47.8	41.8	30	28
J. C. (1)	30/M	Polycystic disease	50.6	40.3	24	19
J. C. (2)			72.0	54.0[c]	16	17
L. H.	65/M	Unilateral kidney	67.3	55.3	14	17
N. D.	35/F	Chronic pyelonephritis	4.3	4.1	78	68
T. M.	21/M	Chronic glomerulonephritis	8.2	7.1	66	82
W. B.	31/M	Lupus nephritis	11.0	6.1	80	131
J. J.	30/M	Interstitial nephritis	12.0	5.4	73	94
J. P. (1)	24/F	Chronic glomerulonephritis	5.5	5.0	47	54
J. P. (2)			4.2	3.5	64	62
P. N.	20/M	Interstitial nephritis	21.0	24.0	38	39
Mean			28	22	48	56
± SEM			±8	±6	±7	±11
P			<0.05		<0.5	

[a] Diagnosis confirmed by histological examination of tissue obtained either by renal biopsy or at surgery.
[b] Endogenous creatinine clearance used as an estimate of glomerular filtration rate unless clearance less than 10 ml/min when the *urea clearance + creatinine clearance/2* was used.
[c] There was no apparent explanation for the improved renal function during the second study.

Table 2. Effect of sodium restriction on body weight, total body water, extracellular fluid volume and plasma volume

Patient	Weight *kg*		Total body water *liters*		ECF volume *liters*		Plasma volume *ml*	
	normal sodium	low sodium	normal sodium	low sodium	normal sodium	low sodium	normal sodium	low sodium
W. M.	83.0	82.0	38.3	37.5	11.2	10.9	2841	2962
J. C.	83.7	80.5	40.2	38.8	11.0	11.0	3248	2946
L. H.	80.0	78.5	35.8	34.0	12.2	11.5	4013	3542
N. D.	37.0	37.4	19.2	18.6	7.2	7.0	2414	2275
T. M.	65.7	63.7	41.1	39.6	14.0	12.0	4356	3491
W. B.	56.7	54.5	30.0	28.0	9.6	9.0	3448	3125
J. J.	60.9	60.2	39.1	37.6	11.5	11.3	3350	3295
Mean	66.7	65.3	34.8	33.4	11.0	10.4	3381	3091
± SEM	±7.0	±6.2	±3.0	±2.9	±1.0	±0.7	±249	±163
P	<0.02		<0.001		<0.10		<.01	

in these patients decreased significantly[1] from 28 to 22 ml/min. The increase in mean blood urea nitrogen from 48 to 56 mg/100 ml during the period of sodium restriction was not significant. Sodium restriction was associated with a significant reduction in mean body weight from 66.7 to 65.3 kg. Volume measurements in seven of the nine patients revealed a significant, though modest, diminution in total body water in all, and a reduction of extracellular fluid and plasma volume in six of the seven patients. None of the patients developed symptoms of hypovolemia during periods of sodium restriction and a constant fluid intake.

Effect of prolonged sodium restriction on sodium and potassium metabolism (Table 3, Fig. 2). The mean daily sodium intake prior to sodium restriction was 138 mEq and the mean duration of these control periods was eleven days (range: 7 to 15 days). The mean daily sodium intake during the period of sodium restriction was 11 mEq and the mean duration of sodium restriction was 18 days (range: 8 to 25 days). In eight of the nine patients, sodium restriction was discontinued when the minimal urinary sodium concentration was achieved. In these eight patients, although the achievement of a minimal urinary sodium concentration was delayed from 8 to 25 days, sodium balance was eventually achieved in each patient. In the ninth patient (J.P.), the urinary sodium concentration remained high and severe hyponatremia developed rapidly. For this reason, dietary sodium restriction was discontinued after nine days in this patient (Fig. 2). Fecal losses of sodium were generally insignificant during periods of both normal and low sodium intake. The mean daily negative sodium balance for the nine patients was 21 mEq, and an average negative cumulative sodium balance of −378 mEq was noted during the period of sodium restriction (mean duration: 18 days). Sodium restriction was associated with a slight but significant diminution in mean plasma sodium concentration from 141 to 136 mEq/liter, including the marked hyponatremia in J.P. (138 to 123 mEq/liter). Diurnal variations in urinary sodium excretion were not observed in any of the nine patients and the 24 hour urine volume was similar during periods of normal and low salt intake. Spironolactone was administered to three patients as the low sodium intake was continued (Table 4). Aldosterone inhibition by spironolactone was associated with an increase in urinary sodium concentration and a decrease in urinary potassium

[1] Paired student "t" test: a P value < 0.05 was considered to be statistically significant.

Table 3. Effect of sodium intake

Patient	Na intake *mEq/day*		Duration *Days*		V *ml/day*		Minimal $U_{Na}V$ on low sodium intake *mEq/day*	$U_{Na}V$ [a] *mEq/day*		Fecal Na losses *mEq/day*	
	Normal Na	low Na	normal Na	low Na	normal Na	low Na		normal Na	low Na	normal Na	low Na
W. M.	169	21	8	11	2479	2506	5	134	26	1.5	3.2
L. H.	162	12	11	23	2146	2419	4	146	23	–	0.7
N. D.	75	10	12	25	1071	1294	15	48	22	–	0.2
T. M.	146	10	12	24	1528	1548	7	102	25	1.2	0.8
J. P.	88	9	7	8	1164	1122	34	67	44	11.0	2.4
J. C.	173	11	11	15	2368	2717	15	162	50	8.6	2.0
P. N.	190	12	10	19	2763	3083	6	161	45	5.3	0.5
J. J.	123	8	13	20	1798	1494	10	121	28	0.3	0.7
W. B.	113	10	15	21	1480	1293	10	113	20	0.7	1.3
Mean	138	11	11	18	1866	1942	12	117	31	4.0	1.3
± SEM	±13	±1	±1	±2	±201	±245	±3	±13	±4	±16	±0.3
P					<0.1			<0.001		<0.1	

[a] Mean values for entire duration of normal and low sodium periods.
[b] Fecal sodium and potassium losses were not measured and are therefore not accounted for in the balance figures.

concentration in all three patients. Free-water clearance was decreased in two of the three patients. In the same three patients mineralcorticoid administration (9-α-fluorohydrocortisone in J.C. and P.N.; desoxycorticosterone acetate in J.J.) during a normal sodium intake was associated with a decrease in urinary sodium concentration and an increase in urinary potassium concentration and free-water clearance. During the period of sodium restriction a modest decrease in GFR occurred in all three patients during the administration of spironolactone. Mineralocorticoid administration during a normal sodium intake

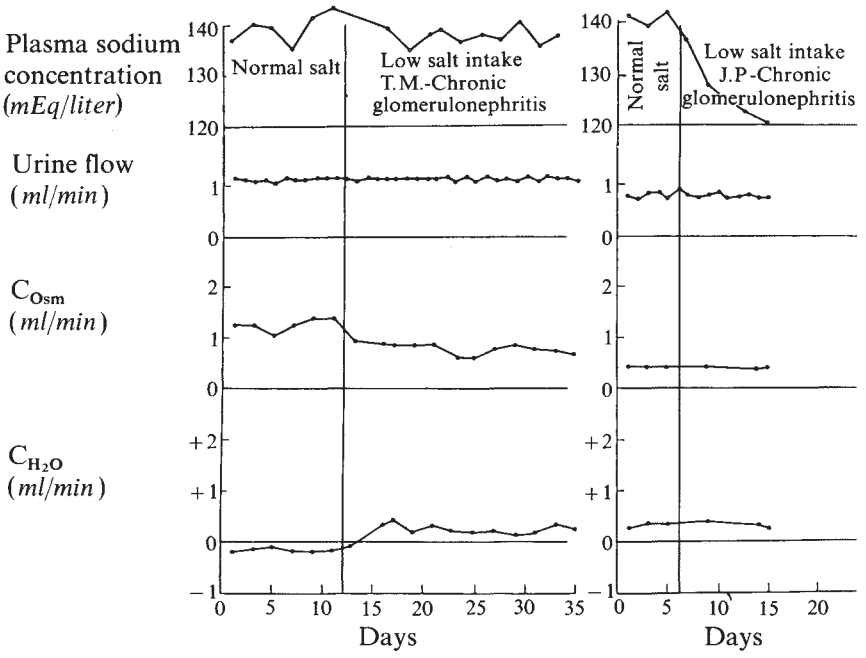

Fig. 2. *Effects of prolonged sodium restriction on plasma sodium concentration, urine flow,* C_{Osm} *and* C_{H_2O}. The patient on the left (T.M.) demonstrated the ability during sodium restriction to diminish C_{Osm} and increase C_{H_2O} as V and P_{Na} remained unchanged. The patient on the right (J.P.) with "salt-losing nephritis" was unable to diminish C_{Osm} and increase C_{H_2O} during sodium restriction and thus rapidly developed hyponatremia.

on sodium and potassium balances

Mean daily Na balance *mEq/day*		P_{Na} *mEq/liter*		K intake *mEq/day*	U_KV *mEq/day*		Fecal K losses *mEq/day*		Mean daily K balance *mEq/day*		P_K *mEq/liter*	
normal Na	low Na	normal Na	low Na		normal Na	low Na	normal Na	low Na	normal Na	low Na	normal Na	low Na
+33.5	− 8.2	144	139	81	66	65	13	27	− 2	−11	5.1	4.5
+16.0[b]	−11.7	133	134	96	92	87	—	5	+ 4[b]	+ 4	4.5	5.8
+27.0[b]	−12.2	146	138	57	34	38	—	6	+23[b]	+15	5.4	5.5
+32.8	−15.8	142	139	47	37	47	7.0	5.5	+ 3	− 5.5	4.5	3.6
+10.0	−37.4	138	123	60	9	15	30	29	+21	+16	6.4	6.1
+ 4.4	−41.0	142	138	84	68	57	21.5	15	− 5.5	+12	3.9	4.1
+33.7	−33.5	144	142	81	50	62	14	10	+17	+ 9	4.7	4.7
+ 1.7	−20.7	145	143	33	26	30	7	7	0	− 4	4.4	5.1
− 0.7	−11.3	138	132	29	28	24	8	8	− 7	− 3	4.6	3.9
17.6	−21.3	141	136	63	46	47	14.4	12.5	6	4	4.8	4.8
± 5	± 4	±1	±2	±8	±9	±8	±3	±3	± 4	± 3	±0.2	±0.3
<0.001		<0.05			<0.1		<0.1[c]		<0.1		<0.1	

[c] "t" test performed only on studies with both normal and low sodium values.

Table 4. Effects of spironolactone and mineralocorticoid administration

Patient	V *ml/min*		U_{Na} *mEq/liter*		U_K *mEq/liter*		C_{H_2O} *ml/min*		P_{Na} *mEq/liter*		P_K *mEq/liter*	
	Cont[a]	Spiron[b]	Cont	Spiron	Cont	Spiron	Cont	Spiron	Cont	Spiron	Cont	Spiron
Spironolactone administration												
J. C.	2.05	1.90	12	29	22	18	+1.09	+0.73	139	136	3.8	4.4
P. N.	1.92	2.22	4	27	24	15	+0.96	+1.16	138	139	4.7	5.3
J. J.	0.81	0.96	7	54	28	12	+0.22	+0.04	142	137	4.6	5.2
	Cont[c]	Mineral[d]	Cont	Mineral	Cont	Mineral	Cont	Mineral	Cont	Mineral	Cont	Mineral
Mineralocorticoid administration												
J. C.	1.89	1.51	64	30	27	43	+0.036	+0.083	145	144	4.2	3.7
P. N.	2.05	1.83	65	27	12	40	−0.051	+0.423	137	142	5.1	4.7
J. J.	1.24	1.20	64	49	17	27	+0.158	+0.168	139	142	4.6	4.8

[a] Cont = Mean values of last 3 days of low sodium intake prior to the diluting and concentrating tests.
[b] Spiron = Mean values after 3 to 5 days of spironolactone treatment and continued low sodium intake.
[c] Cont = Mean value of last 3 days of normal sodium intake prior to the diluting and concentrating tests.
[d] Mineral = Mean values of first 3 days of mineralocorticoid treatment on normal sodium intake.

Table 5. The effect of sodium intake on solute-free water reabsorption (T^cH_2O) during a mannitol diuresis

Patient	Time *min*	V *ml/min*		U/P_{Osm}		C_{Osm} *ml/min*		T^cH_2O *ml/min*	
		normal	low	normal	low	normal	low	normal	low
J. C.	0	0.83	1.03	1.20	1.07	1.00	1.10	+0.17	+0.07
Polycystic	30	4.60	3.23	1.20	1.02	5.52	3.29	+0.92	+0.06
disease	60	6.61	3.80	1.15	1.00	7.60	3.82	+0.99	+0.02
	90	4.14	3.26	1.17	0.96	4.84	3.12	+0.70	−0.14
P. N.	0	1.52	1.53	1.10	0.74	1.67	1.13	+0.15	−0.40
Interstitial	30	2.91	2.63	1.06	0.65	3.08	1.71	+0.17	−0.92
nephritis	60	3.66	3.44	1.05	0.75	3.83	2.59	+0.17	−0.85
	90	3.40	2.08	1.07	0.75	3.63	1.56	+0.23	−0.52
J. J.	0	1.25	0.90	0.96	0.94	0.86	1.17	+0.27	−0.04
Interstitial	30	1.80	2.39	0.93	0.90	1.67	2.15	−0.13	−0.24
nephritis	60	3.78	2.90	0.85	0.90	3.19	2.60	−0.59	−0.30
	90	3.55	2.80	0.92	0.87	3.25	2.42	−0.30	−0.38
	120	2.34	2.33	0.95	0.92	2.23	2.14	−0.13	−0.19
Mean ± SEM	0	1.20 ±0.2	1.15 ±0.2	1.09 ±0.1	0.92 ±0.1	1.18 ±0.2	1.13 ±0.02	+0.20 ±0.04	−0.12 ±0.14
	30–120	3.68 ±0.4	2.87 ±0.2	1.04 ±0.04	0.87 ±0.04	3.88 ±0.5	2.49 ±0.3	+0.20 ±0.20	−0.35 ±0.1
P	0	<0.1		<0.1		<0.1		<0.1	
	30–120	<0.05		<0.01		<0.01		<0.01	

was associated with a modest increase in GFR in all three patients.

Potassium balance was not altered consistently and the plasma potassium concentration did not differ during the periods of normal and low sodium intake. Fecal potassium loss was not affected by the sodium intake but in some cases rather significant losses were present on both normal and low sodium intakes. In one patient (J.P.) with marked renal impairment (GFR: 3.5 to 5.2 ml/min) and severe hyponatremia during sodium restriction, approximately 50% of the daily potassium intake was excreted in the feces.

Effect of prolonged sodium restriction on renal concentrating and diluting capacity (Figs. 3 to 5, Table 5). Impairment of renal concentrating ability was demonstrated in every patient during the period of normal sodium intake (Fig. 3). In five patients (J.P., J.J., N.D., W.M., and P.N.) the maximal urinary osmolality remained below that of plasma after fluid deprivation and vasopressin administration, i.e., so-called vasopressin-resistant hyposthenuria [11]. Prolonged sodium deprivation and decreased solute excretion was not associated with improved concentrating ability in any of the nine patients. In fact, in nine of the eleven studies the maximal urinary osmolality was lower during the period of low sodium intake. The maximal urinary osmolality averaged 350 ± 39 mOsm/kg on a normal sodium diet, and 281 ± 20 mOsm/kg on a low sodium diet ($P < 0.05$). The largest decrease in urinary osmolality was observed in the patient with a unilateral kidney and the least impairment of glomerular filtration rate (L.H.). Maximal T^cH_2O formation was examined during mannitol diuresis in three patients on both a normal and low sodium intake (Table 5). On a low sodium intake, hypotonic urine was excreted by all three patients, i.e., T^cH_2O formation became negative. T^cH_2O formation became negative in only one patient (J.J.) during mannitol diuresis on a normal sodium intake. The addition of mineralocorticoid to the normal sodium intake did not affect either maximal urinary osmolality or T^cH_2O formation.

The effect of sodium intake on diluting ability is shown in Fig. 4. The minimal urinary osmolality on

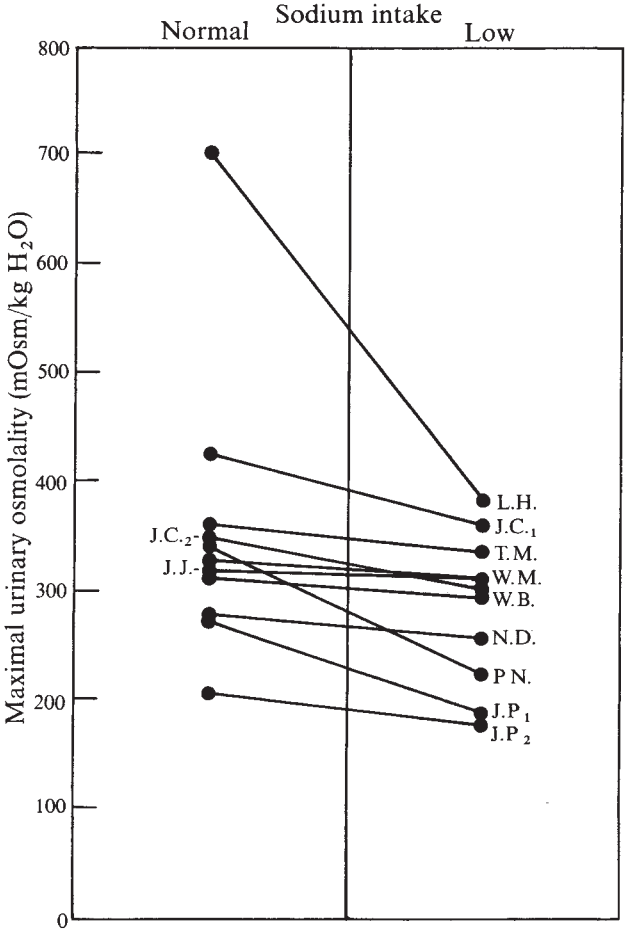

Fig. 3. *Effect of prolonged sodium restriction on maximal urinary osmolality.* Maximal urinary osmolality diminished in 9 of 11 patients during sodium restriction.

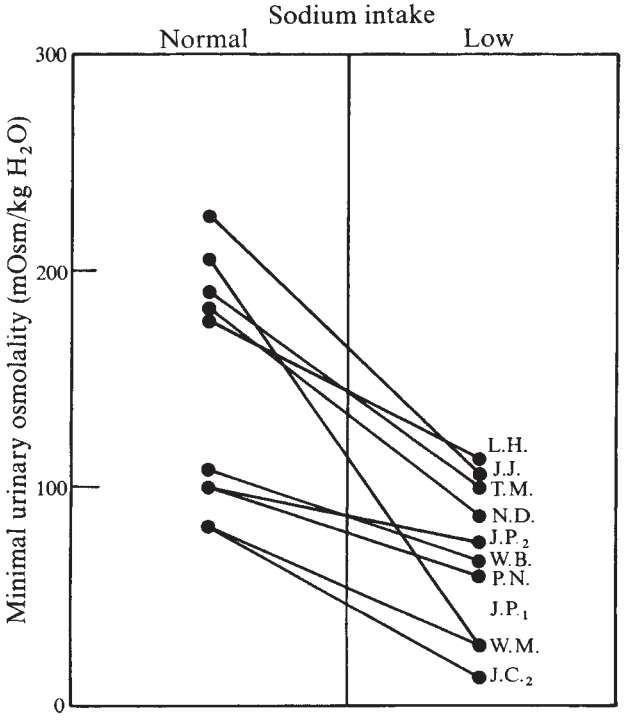

Fig. 4. *Effect of prolonged sodium restriction to improve diluting capacity.* The minimal urinary osmolality achieved during an acute water load was lower in each study during low sodium as compared to normal sodium intake.

a normal sodium intake was high in all nine patieuts (range: 80 to 230 mOsm/kg), but it was significantly lower during sodium restriction. The minimal osmolality averaged 180±9 mOsm/kg on the normal sodium intake and 124±1 mOsm/kg on a low sodium intake ($P<0.001$). In three patients the administration of mineralocorticoid during a normal sodium intake was associated with a diminution in minimal urinary osmolality, and the administration of spironolactone during low sodium intake was associated with an increase in minimal urinary osmolality (Fig. 5).

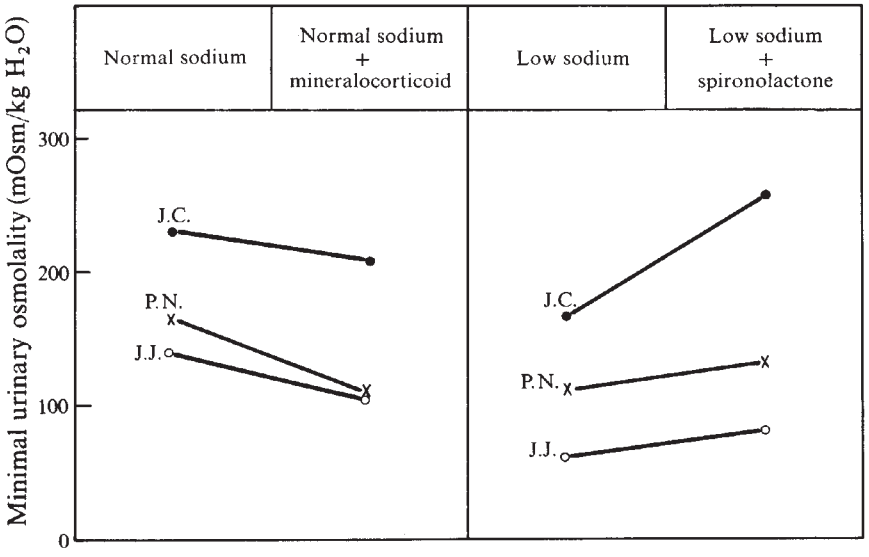

Fig. 5. *Role of mineralocorticoid in improvement of diluting capacity during sodium restriction.* The administration of 9-α-fluorohydrocortisone or desoxycorticosterone decreased minimal urinary osmolality during a normal sodium intake, while the administration of spironolactone increased minimal urinary osmolality during a low sodium intake.

provide strong evidence for an aldosterone-induced enhancement of sodium reabsorption during sodium restriction in chronic renal disease. In addition, the exogenous administration of mineralocorticoids was found to mimic the urinary effects of sodium restriction even in the presence of a normal sodium intake (Table 4). Taken together, therefore, the present results seem to suggest strongly that aldosterone is of physiological importance in the control of sodium metabolism in chronic renal disease. However, one must acknowledge the possibility that alterations in aldosterone activity may be of physiological importance in the regulation of sodium excretion in patients with moderate renal impairment, but that it exerts very little influence in patients with severe end-stage renal impairment. In this regard, many of the studies of Slatopolsky et al [6] which indicated that a "third factor" might be involved in the regulation of sodium excretion in chronic renal failure were performed in patients with severe renal impairment. In the present study the glomerular filtration rates were 54, 24 and 5 ml/min in the three patients who received spironolactone during dietary sodium restriction. In all three patients a large increase in urinary sodium excretion was observed during the administration of spironolactone and, in fact, the largest natriuresis was observed in the patient (J.J.) with the lowest filtration rate. These present results are therefore compatible with the thesis that aldosterone is an important regulator of urinary sodium excretion at all levels of glomerular filtration rate in patients with chronic renal disease. However, before this tentative conclusion can be accepted

Discussion

The present results suggest that alterations in aldosterone activity may be of physiological importance in the renal response to sodium restriction in patients with chronic renal disease. The observed increase in urinary aldosterone excretion during sodium restriction in these patients is compatible with such a thesis. Nevertheless, this observation alone was insufficient to establish a cause and effect relationship between increased aldosterone excretion and decreased urinary sodium excretion. For this reason, studies were undertaken in three patients to assess the effect of a spironolactone-mediated inhibition of the action of aldosterone. In each instance urinary sodium excretion increased substantially during the administration of spironolactone despite continued dietary sodium restriction (Table 4). Since spironolactone is thought to exert its effect on renal tubular sodium reabsorption via direct inhibition of the action of aldosterone [12], the present results would seem to

finally, additional studies of patients with severe renal impairment will be required. It should also be emphasized that the demonstration of a physiological role of aldosterone in the regulation of sodium excretion in chronic renal disease in no way precludes an additional role of other factors, such as changes in glomerular filtration rate and the activity of "third factor". Instead an interaction between all of these factors seems most likely.

The possibility that aldosterone might not exert a significant influence on sodium excretion in chronic renal disease was based, at least partially, on the finding that the majority of patients with severe chronic renal disease may exhibit an increased aldosterone secretory rate [8, 9]. These results, [8, 9] however, may be related to methodological problems involved in measuring aldosterone secretory rates in patients with chronic renal disease rather than being indicative of increased aldosterone production. Cope and Pearson [8] have reported that, in contrast to normal subjects, the excretion of the metabolite that is used to measure aldosterone secretion may be delayed considerably longer than 24 hours in patients with chronic renal disease. Since measurements of aldosterone secretion are based on the excretion of the majority of the measured metabolite in 24 hours after the injection of isotope-labeled aldosterone, measurements in chronic renal disease are difficult to interpret even when corrections for the delayed excretion of the metabolite are attempted [8]. Hayslett et al [13] have used an *in vitro* assay method of adrenal glands in azotemic rats to assess aldosterone production, thereby avoiding any methodological error related to impaired renal excretion. These investigators [13] failed to find any evidence of increased aldosterone production in this experimental model of renal failure.

In the present study repeated measurements of aldosterone excretion in the same patient were used as a qualitative index of adrenal responsiveness to salt restriction in patients with chronic renal disease. Steady-state conditions were insured by maintaining the patients on the same sodium intake for at least one to two weeks prior to measuring the 24 hour excretion rate of aldosterone. During both normal and low dietary sodium intake three consecutive daily measurements were obtained. Under such steady-state conditions and assuming that endogenous aldosterone metabolism remains unaltered, the observed increase in aldosterone excretion should provide a reasonable qualitative index of an increase in aldosterone production. The observed decrease in glomerular filtration rate during sodium restriction should tend, if anything, to decrease the measured rate of aldosterone excretion; thus changes of filtration rate would not seem to provide an explanation for the observed increase in aldosterone excretion.

Although it was not our purpose to examine whether the majority of patients with chronic renal disease are in a state of "hyperaldosteronism", the demonstration of a normal adrenal responsiveness to salt restriction in the present patients is most compatible with the results of Hayslett et al [13] which suggested that aldosterone production was normal in uremia. In the present study, aldosterone excretion was found to be within the range of normal during ingestion of normal sodium intake. It should be emphasized, however, that a normal rate of aldosterone production could be associated with a normal rate of aldosterone excretion by diseased kidneys in the presence of an elevated plasma concentration of aldosterone. Nevertheless, even if the plasma concentration of aldosterone should be found to be elevated in some patients with chronic renal disease, the present results would seem to somewhat mute the physiological significance of such a finding. In this regard, the most important question concerning the physiological aspects of aldosterone metabolism in chronic renal disease would seem to be whether aldosterone still exerts a significant influence on renal adjustments to alterations in dietary sodium intake. The present finding that the decrease in urinary sodium excretion during sodium restriction may be reversed by spironolactone, and duplicated on a normal sodium intake by exogenous mineralocorticoid administration, supports such a physiological role of aldosterone in chronic renal disease. The concept that chronically diseased kidneys remain responsive to humoral substances which regulate tubular reabsorption is not without precedent. Slatopolsky et al [14] have recently shown that the regulation of tubular phosphate reabsorption in chronic renal disease remains under the control of parathormone activity.

Although increased aldosterone activity, enhanced distal sodium reabsorption and increased free-water excretion were consistently observed during sodium restriction in eight patients, in one patient (J.P., Fig. 2) sodium excretion did not diminish significantly and free-water clearance did not increase during sodium restriction. In the presence of a constant fluid intake and urine output this combination of events was associated with the rapid development of hypo-

natremia such as that observed in salt-losing nephritis [15–17]. In this same patient sodium restriction on two occasions was associated with a significant increase in aldosterone excretion. Therefore, in contrast to the other eight patients, the presence of a physiological role for aldosterone could be questioned in this patient.

The importance of aldosterone in potassium metabolism in chronic renal disease was also examined in the present study. Urinary potassium excretion and the plasma potassium concentration were not significantly different during normal or low sodium intake in the present patients. In view of the findings of increased aldosterone activity and diminished sodium excretion during sodium restriction, a concomitant increase in potassium excretion might have been expected if the rate of sodium delivery to the distal nephron remained unchanged. The constancy of urinary potassium excretion during sodium restriction thus suggested that a decreased rate of sodium delivery to the distal tubule occurred during sodium restriction, and that it obscured the tendency of increased aldosterone activity to increase potassium secretion.[2] The decreased rate of glomerular filtration provided a probable mechanism whereby the rate of distal sodium delivery may have been decreased during sodium restriction, but an additional effect of increased proximal sodium reabsorption cannot be excluded [18]. The effect of spironolactone to decrease potassium excretion and increase plasma potassium concentration during sodium restriction supported the hypothesis that the constancy of urinary potassium excretion, in spite of decreased distal sodium delivery during sodium restriction, was at least partially related to increased aldosterone activity. In contrast to the renal effect of aldosterone, the excessive fecal losses of potassium in the present patients were not altered during sodium restriction and increased aldosterone activity. This finding confirms the earlier work of Hayes et al [19, 20] who were unable to demonstrate an effect of either sodium restriction or spironolactone on fecal potassium losses in patients with chronic renal disease.

The importance of aldosterone in water metabolism in chronic renal disease was also investigated in the present study. Since changes of fluid [21] and protein intake [22] may influence renal concentrating capacity, the present patients were maintained on the same fluid and protein intake throughout the study. Prolonged sodium restriction was found to be associated with a diminution in maximal urinary osmolality and solute-free water reabsorption. Although it has been demonstrated that sodium restriction of three days duration does not affect maximal urinary osmolality in patients with impaired renal function [23], sodium restriction in normal man [24] and dog [25] has been shown to decrease solute-free water reabsorption. The present observations provide the first demonstration of an effect of sodium restriction on the renal concentrating mechanism in chronic renal disease. This defect in renal concentrating capacity during sodium restriction did not seem to be related to increased aldosterone activity since it could not be produced by the administration of exogenous mineralocorticoid in the presence of normal sodium intake. Although Giebisch and Lozano [26] found that the chronic administration of aldosterone was associated with a diminution in solute-free water reabsorption in dogs, the diminished plasma potassium concentration which was observed in their experiments could have been responsible for the renal concentrating defect [27]. In the present patients, prolonged sodium restriction was associated with a diminution in solute-free water reabsorption in the absence of any change in the plasma potassium concentration.

A decreased delivery of sodium to the thick ascending limb of the loop of Henle, as a result of the diminution in filtration rate, is a possible mechanism for the diminution in renal concentrating capacity during sodium restriction. There is, however, experimental evidence that a decrease in glomerular filtration rate, of a similar degree as that observed in the present study, is associated with an increase, not a decrease, in urinary osmolality in experimental animals undergoing a water diuresis [28, 29]. In hydropenic animals, however, a decrease in sodium delivery to the ascending limb could conceivably decrease rather than increase urine osmolality. In either case, further studies are indicated to define the mechanism of the diminution in renal concentrating capacity that is associated with sodium restriction in chronic renal disease. The present results, however, suggest that this effect is not a result of increased aldosterone activity during sodium restriction.

In contrast to the defect in renal concentrating capacity, an improved diluting capacity was observed

[2] Although there is now experimental evidence that the tubular reabsorption of sodium and the tubular secretion of potassium are not necessarily coupled, altered distal sodium delivery in the presence of supraphysiological doses of aldosterone is consistently associated with parallel changes in urinary potassium excretion [4].

during sodium restriction. The improved diluting capacity could be reversed by the administration of spironolactone despite continued sodium restriction, and it could be duplicated by the administration of exogenous mineralocorticoid and a normal sodium intake. These findings would thus suggest that aldosterone is important in the improved diluting ability during sodium restriction in chronic renal disease. The results however should not be considered to exclude an additional role of diminished solute load per nephron [23].

In summary, the results of the present study suggest that aldosterone is of physiological importance in sodium, potassium and water metabolism in patients with chronic renal disease. The diminution in sodium excretion observed in these patients during sodium restriction was associated with an increase in aldosterone activity, as judged by a qualitively normal increase in aldosterone excretion. This decrease in sodium excretion could be reversed by the administration of spironolactone during continued sodium restriction, and duplicated by the administration of exogenous mineralocorticoid despite a normal sodium intake. Urinary potassium excretion was unaltered during sodium restriction, although the concomitant decrease in glomerular filtration rate suggested a decreased distal delivery of sodium. The kaliuresis and increased plasma potassium concentration during spironolactone administration and sodium restriction suggested that increased aldosterone activity may have allowed a constancy of urinary potassium excretion despite the diminished distal delivery of sodium. Sodium restriction was associated with a diminished maximal urinary osmolality and maximal solute-free water reabsorption which could not be duplicated by exogenous mineralocorticoid administration and a normal sodium intake. However, the improved renal diluting capacity during sodium restriction could be reproduced by the exogenous administration of mineralocorticoid and reversed by spironolactone.

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