"RENAL SALT WASTING"

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A RENAL SALT-WASTING

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- phosphates
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I. Normal Mechanisms of Sodium Reabsorption

Approximately 21000 mEq of sodium are filtered at the glomerulus in normal man in a 24 hour period. Approximately 99.5% of the sodium in this glomerular filtrate is reabsorbed as the filtrate courses through the nephron. The bulk of the filtered sodium is reabsorbed isosmotically in the proximal tubule. In the proximal tubule a fraction of sodium is reabsorbed in exchange for hydrogen ion which is secreted to promote the reabsorption of filtered bicarbonate. The far greater fraction of sodium reabsorbed in the proximal tubule is probably reabsorbed through passive mechanisms based on peritubular capillary osmotic effects and the active reabsorption of glucose and amino acids. The thick ascending limb of Henle is the next major site of sodium reabsorption. Here approximately 10 to 20% of the sodium filtrated at the glomerulus is reabsorbed. This section of the nephron appears to act as the fine modulating mechanism for sodium reabsorption in contrast to the proximal tubule which appears to have a rather coarse adjustment. The mechanism of sodium reabsorption in this is an electrogenic force resulting from active chloride transport. The active chloride pump extends throughout the length of the thick ascending limb and the next site beyond is the aldosterone responsive distal exchange site. The anatomical location of this site is the subject of recent investigation and the nephrology laboratory at Southwestern Medical School has developed new information that this aldosterone responsive site extends into the cortical collecting duct. This site is responsible for the reabsorption of about 2% of the glomerular filtrate. Some have found that the collecting duct plays a role in sodium reabsorption, although the extent and magnitude of this activity is uncertain.

1. Brenner BM: Renal Handling of Sodium. Fed Proc 33:13, 1974

2. Deen WM, Robertson CR and Brenner BM: Glomerular Ultrafiltration. Fed Proc 33:14, 1974

3. Windhager EE: Some aspects of proximal tubular salt reabsorption. Fed Proc 33:21, 1974

4. Kokko JP: Membrane Characteristics Governing Salt and Water Transport in the Loop of Henle. Fed Proc 33:25, 1974

5. Burg M and Stoner L: Sodium Transport in the Distal Nephron. Fed Proc 33: 31, 1974

6. Schrier RW and de Wardener HE: Tubular Reabsorption of Sodium Ion: Influence of Factors Other than Aldosterone and Glomerular Filtration Rate. N Eng J Med 285:1231,1292, 1971

II. Volume Depletion (experimental human salt depletion)

Symptoms and Signs

In 1936, R. A. McCance, before the Royal College of Physicians of London at the Goulstonian Lectures, described a classic series of experiments performed on himself and several volunteer medical students. The design of his experiment was simple. He reasoned that sodium chloride deficiency could be produced best in the normal human by combining a salt free diet with forced sweating. Water losses were replaced. McCance's wife prepared a salt free diet which was designed to provide adequate nitrogen sources. The forced sweating was initiated using a full length radiant heat bath. The subject usually spent about two hours in this heat bath which resulted in fluid losses of two to three liters at a time. The amount of sweat was collected in the chamber and analyzed. Upon emerging from the bath the subject was washed from head to foot with distilled water which was collected and analyzed as well. In addition, all urine and feces were preserved for analysis. Finally, their underclothes which had been previously washed many times were analyzed for insensible losses of chloride. His description of the signs and symptoms that he and his collaborators observed during that time makes fascinating reading.

> "Salt deficiency produces an obvious change in the facies. The temporal hollows in the cheeks fall in, the eyes seem tired and sunken --- I think we all looked rather worn and ill towards the end of our experiment --- There is always a loss of weight to which I shall refer again later. We have all noticed a peculiar sensation in the mouth, which is present all day long. This is not thirst, although Miss Edwards considered that it was so and drank freely in her attempts to obtain relief. All food seemed to be tasteless --The characteristic flavors are there but they are blunted. Anorexia and nausea are prominent symptoms. I was never very hungry and I think this is true of all the other victims, but Niven and I always managed to get through the prescribed rations for the day --- Indeed, the nausea is not noticeably related to food, and my feelings of sickness often passed off after I had managed to force a little food down my throat --- We all noticed that our water metabolism was not normal. After drinking a large water load, no diuresis would develop at that time, but then hours later, possibly the next night the diuresis would begin --- We all suffered a good deal from cramps except Miss Edwards, who escaped. I think her deficiency was relatively slight. These cramps are most characteristic. They are not the localized type described by Moss in miners and stokers. Our cramps were relatively mild and easily controllable, but any muscle suddenly brought into action was liable to spasm. Coughing produced cramps all around the head as did yawning produce a cramp in the floor of the mouth. I think the most characteristic were the cramps in the fingers that came on whenever one tried to pipette or use a pair of forceps --We all suffered of excessive fatigue and a general sense of exhaustion. Towards the end, Whitteridge felt wretched enough to go to bed as soon as the days experiments were over. Whitteridge and Niven both got into the extraordinarily interesting state in which they were content to sit and do nothing in a chair sometimes for hours on end. They all commented on feeling slow in the head. We have not noticed any change in the resting pulse rate, but volume became small."

The intake of these investigators of sodium was low, somewhere between 40 and 70 mg/day. Total sodium depletion was approximately 1000 mEq. The urine in each of these subjects, after about four days contained less than one mEq of sodium in 24 hours. The subjects developed mild hypochloremia during the course of the experiments but did not seem to develop profound hyponatremia. Perhaps there was some analytic problem with sodium at that time. For example, one subject's (DW) initial sodium was 154 mEq/L and by the end of the deficiency period, his sodium was 139 mEq/L.

These studies then give us considerable insight into what we might look for in the salt depleted subject. The one observation that McCance stressed that is at variance with subsequent observations was the absence of a fall in blood pressure. His subjects did show a rise in the urea nitrogen of the plasma during the course of sodium deficiency, but he did not comment on the measurement of blood pressure in the upright position. He did note that the pulse became faint and that its rate increased.

A decrease in plasma volume was found by McCance and more dramatically found in subsequent studies in heat exhaustion. McCance's subjects may not have shown hypotension because of the moderate degree of salt depletion or rather because an observation was not made in the upright position. The observation of salt depleted people in a tropical climate subsequently supported the view that hypotension was an important part of the salt depletion syndrome (Marriott).

7. McCance RA: Medical Problems in Mineral Metabolism. Lancet 1:643,704,765, 823, 1936

8. Marriott HL: Water and Salt Depletion. Brit Med J i:245,285,328, 1947

9. Black DAK, Platt R and Stanbury SW: Regulation of Sodium Excretion in Normal and Salt-depleted subjects. Clin Sci 9:205, 1950

III. Renal Salt Wasting

A. Primary Salt Wasting with Intact Renal Architecture

Proximal Tubular Defects

The occurrence of a salt wasting state after the release of urinary tract obstruction is relatively infrequent. The majority of cases undergo an osmotic diuresis secondary to retained urea loads and/or a spontaneous diuresis of retained fluids. This point has been emphasised by Maher. Eiseman, Wilson, and Muldowney have each described cases which fit most of the criteria for continued salt wastage after the relief of urinary tract obstruction.

10. Maher JF, Schreiner GE and Waters TJ: Osmotic Diuresis Due to Retained Urea after Release of Obstructive Uropathy. N Eng J Med 268:1099, 1963

11. Eiseman B, Vivion C and Vivian J: Fluid and Electrolyte Changes Following the Relief of Urinary Obstruction. J Urol 74:222, 1955

12. Wilson B, Reisman DD and Moyer CA: Fluid Balance in the Urological Patient: Disturbances in the Renal Regulation of the Excretion of Water and Sodium Salts Following Decompression of the Urinary Bladder. J Urol 66:805, 1951

13. Muldowney FP, Duffy GJ, Kelly DG et al: Sodium Diuresis after Relief of Obstructive Uropathy. N Eng J Med 274:1294, 1966

The mechanism for salt wasting in this state has been subject to recent investigations. Massry, Bricker, and Falls have studied patients with a post obstructive diuresis and concluded that it appears the defect in sodium reabsorption resulting in the sodium diuresis resided in the proximal tubule. Depression of the reabsorption of other ion species and glucose reabsorbed in the proximal tubule besides sodium have been observed by several investigators (Falls, White).

14. Massry SG, Schainuck LI, Goldsmith C et al: Studies on the Mechanism of Diuresis after Relief of Urinary-tract Obstruction. Ann Intern Med 66: 149, 1967

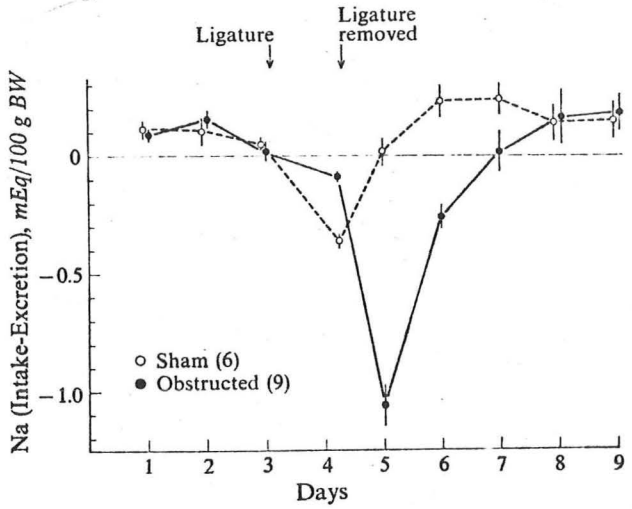
15. Bricker NS, Shwayri EI, Reardan JB et al: An Abnormality in Renal Function Resulting from Urinary Tract Obstruction. Am J Med 23:554, 1957

16. Falls WF and Stach WK: Post obstructive Diuresis. Am J Med 54:404, 1973

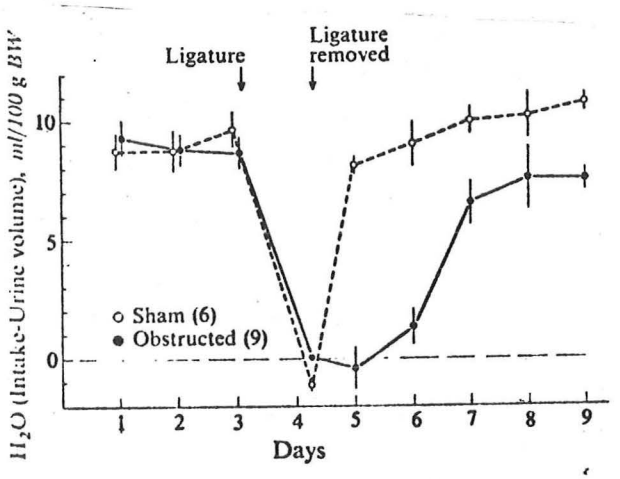
17. White MG, unpublished observation.

Finkle has found that after the relief of acute obstruction there is a pronounced rise in cortical blood flow utilizing the krypton washout technique. These superficial cortical nephrons have a low sodium and chloride reabsorbing capacity and Finkle would presume that the sodium diuresis was based on this redistribution of blood flow. These observations were given further support by Wilson, who found a disproportionately high surface nephron to whole kidney glomerular filtration rate present in most of the animals after the relief of obstruction. His animals however did not show a post obstructive diuresis. Bercovitch found after the relief of 24 hours of complete unilateral ureteral obstruction in the dog that the experimental kidney was characterized by a decrease in filtration rate and increase in fractional and often absolute excretion of sodium both before and after the administration of mannitol. He also noted that the reabsorptive rate for glucose was depressed in the post obstructive kidney. Yarger in micropuncture studies on the rat found a striking diuresis after the relief of of obstruction in rats with bilateral ureteral obstruction. Fraction reabsorption of the proximal tubule was normal in these animals as measured by tubular fluid to plasma inulin ratios. These authors felt that the site of the impaired sodium reabsorption was distal to the proximal tubule. McDougal and Wright studied two groups of rats, one in which a ligature was placed around the trigone of the bladder occluding both ureters and the second group were sham operated. Other manipulations were done as well but essentially, this study showed that the clearance of inulin was reduced in the previously obstructed kidney while the excretion of sodium, potassium and solute was increased. The sodium and water reabsorption were decreased in the proximal and distal nephrons while distal nephron potassium excretion was increased. An important observation was that microinjection studies showed there was an increase permeability both to mannitol and inulin when these substances were injected in both proximal and distal surface nephrons. The accompanying figures from the paper of McDougal show the continued excretion of sodium after release of the diuresis in the obstructed animals generating a negative deficit and the persistent negative deficit of water and the depression in creatinine clearance in these animals. The last two figures show that when both mannitol and inulin were injected into the surface tubules a decrease

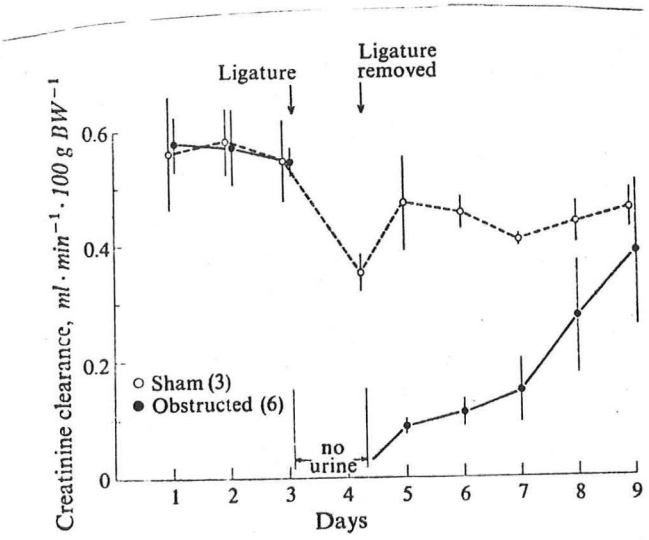
in recovery was found in the collection of the ureteral urine. These studies showing a change in permeability characteristics of the nephron suggest that substantial back flux of sodium may be an important factor in the increase of sodium excretion. That is, that sodium that is reabsorbed flows back into the nephron lumen resulting in decreased net sodium sodium reabsorption.



Daily differences between Na intake and combined urinary and fecal Na excretion.

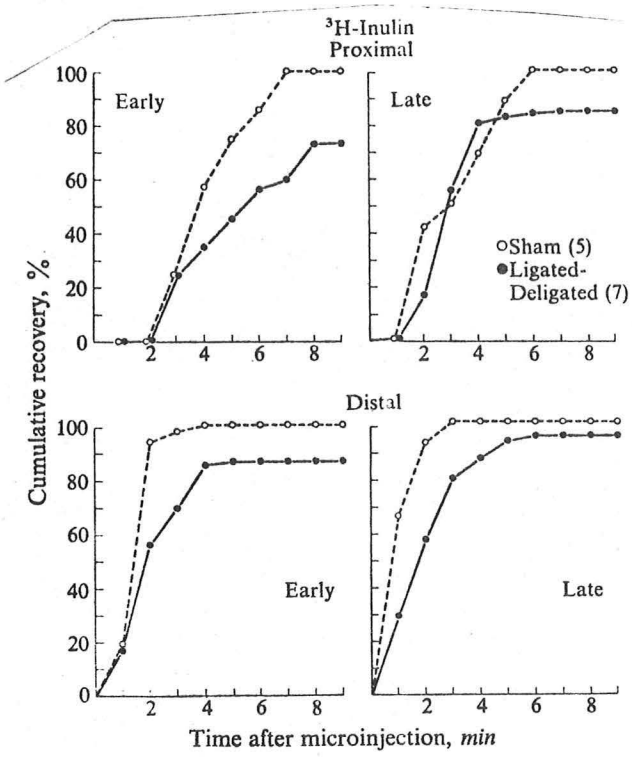


Daily differences between water intake and urinary volume. Points indicate means, vertical lines indicate ± 1 SE, parentheses indicate number of rats.

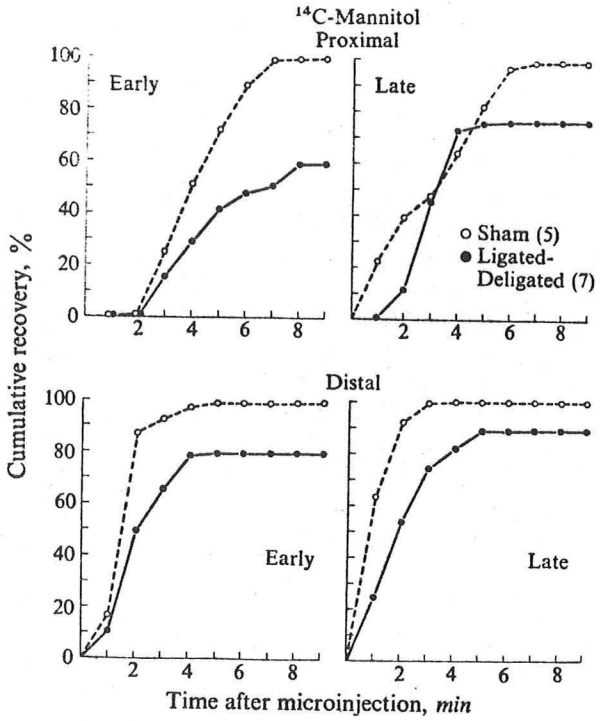


Creatinine clearance before and after bilateral ureteral obstruction.

From Ref. 22



Cumulative recovery in successive 1.0 min ureteral urine collections of ^{3}H-inulin injected into surface tubule segments. Points are mean values for the number of injections indicated.



Cumulative recovery in successive 1.0 min ureteral urine collections of ^{14}C-mannitol injected into surface tubule segments.

From Ref. 22

18. Finkle AL, Karg SJ and Smith DR: Parameters of Renal Functional Capacity in Reversible Hydroureteronephrosis in Dogs. Invest Urol 7:215, 1969

19. Wilson DR: Micropuncture Study of Chronic Obstructive Nephropathy Before and After Release of Obstruction. Kid Intern 2:119, 1972

20. Bercovitch DD, Kasen L and Blann L: The Postobstructive Kidney. Observations on Nephron Function after the Relief of 24 hr of Ureteral Ligation in the Dog. J Clin Invest 50:1154, 1971

21. Yarger WE, Aynedjian HS, and Bank N: A Micropuncture Study of Postobstructive Diuresis in the Rat. J Clin Invest 51:625, 1972

22. McDougal WS and Wright FS: Defect in Proximal and Distal Sodium Transport in Post-obstructive Diuresis. Kid Intern 2:304, 1972

Diuretic Phase of Tubular Necrosis

Whether or not a salt wasting state exists during the diuretic phase of acute tubular necrosis is subject to some controversy. Swan, in a well documented report on a number of patients with acute tubular necrosis, found that when salt was restricted during the developmental phases of the acute tubular necrosis in the anuric or oliguric period that the extent of the diuresis ensuing with the return of renal function was blunted and makes the case along with Merrill that by and large the most frequent reason for profound diuresis occurring during the recovery phase of acute tubular necrosis is the delivery of retained salt and water accumulated during the preceding period of low urinary output. Bull, in an early description of acute tubular necrosis, made two interesting observations; (1) that glycosuria occurred at times of a normal plasma glucose in some recovering patients providing some support that the lesion during the diuretic phase includes at least some defect in proximal mechanisms. In addition (2), he describes one patient who during the early anuric phases of acute tubular necrosis was hypertensive but then with the ensuing diuresis had a decline in weight and a fall in blood pressure to the low normal ranges. There was no other mention of decreased organ perfusion and during this time the urea nitrogen continued to fall. A paper from Hunter points out the dilemma in diagnosing the diuretic salt wasting component of the diuretic phase and the difficulties in administering large amounts of salt to patients suspected of having a salt wasting state.

23. Swan RC, Merrill JP: The Clinical Course of Acute Renal Failure. Med 32:215, 1953.

24. Merrill JP: The Treatment of Renal Failure. New York, Grune & Stratton 1965, Pp 194-199

25. Bull GM, Joekes AM and Lowe KG: Renal Function Studies in Acute Tubular Necrosis. Clin Sci Mol Bio 9:379, 1950

26. Hunter RB and Muirhead EE: Prolonged Renal Salt Wastage in "Lower Nephron Nephrosis". Ann Intern Med 36:1297, 1952

Thick Ascending Limb Defects

Bartter's Syndrome

Several controversies exist in interpreting the data from patients with Bartter's syndrome (hypokalemic, metabolic alkalosis associated with juxtaglomerular hyperplasia). Cannon observed the continued excretion of sodium on a salt restricted diet and felt that sodium wastage was a component of the disease. However, during the time these balance studies were being performed the patient's were receiving extraordinary amounts of potassium chloride supplements. It is likely that the sodium appearing in the urine came from intracellular stores accumulated during a prior state of potassium deficiency. The accompanying figure of a patient with Bartter's syndrome that I studied at the U.S. Army Institute of Surgical Research shows that he was able to reduce his sodium excretion to intake levels and in that sense did not evidence salt wastage. Note that even at the beginning of the salt deprivation period there were certain indices which suggested that he was already volume contracted, that is his plasma renin level was greatly elevated as was the aldosterone

excretion and secretory rate despite severe hypokalemia. With salt restriction, these parameters were further increased and in addition the patient had a fall in blood pressure and decrease in glomerular filtration rate. The elevated plasma renin and plasma aldosterone concentration could be suppressed by volume administration and at the time of volume expansion he excreted sodium at a far faster rate than normal subjects who did not have an elevated plasma renin nor aldosterone level. The conclusion drawn from this data was that Bartter's syndrome is a form of salt wasting of a unique type so that the individual is maintained in a state of chronic hypovolemia, but when subjected to severe sodium restriction these patients are able to eliminate sodium from the urine. Therefore the defect lies beyond the proximal tubule and perhaps beyond certain proximal portions of the thick ascending limb at which point sodium has been completely reabsorbed. Maximum sodium conservation can then occur, but should any sodium reach a somewhat more distal site short, however, of the aldosterone sensitive exchange site it is not reabsorbed but then is presented to the distal exchange site where high levels of circulating aldosterone can exchange it for potassium resulting in the hypokalemia and attendant metabolic alkalosis. Nakada has described a young woman with Bartter's syndrome who could not tolerate a low sodium diet though the specific problems were not detailed and Chaimovitz has described an infant that suggested the defect was somewhere in the distal diluting segment of the nephron. The patient studied by Chaimovitz seemed to be exquisitely sensitive to the effect of chlorothiazide suggesting that its site of action might be the area where the defect of sodium reabsorption occurs.

27. Cannon PJ, Leeming JM, Sommers SC et al: Juxtaglomerular cell hyperplasia and secondary hyperaldosteronism, (Bartter's Syndrome). Med 47:107, 1968

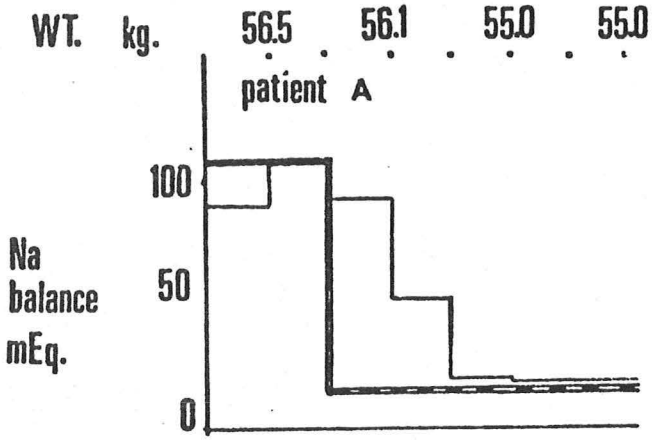
28. White MG: Bartter's Syndrome. A Manifestation of Renal Tubular Defects. Arch Intern Med 129:41, 1972

29. Nakada T, Momose G, Tateno Y et al: Renin-Angiotensin-Aldosterone System of a Woman with Bartter's Syndrome: Juxtaglomerular Cell Hyperplasia Without Hypertension. J Urol 112:293, 1974

30. Chaimovitz C, Levi J, Better OS et al: Studies on the Site of Renal Salt Loss in a Patient with Bartter's Syndrome. Pediat Res 7:89, 1973

BARTTER'S SYNDROME

"RELATIVE SALT WASTING"



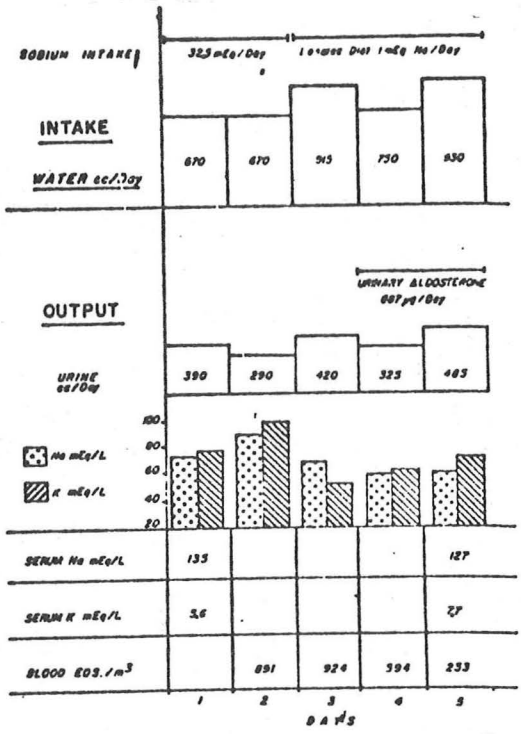
PLASMA RENIN ACTIVITY ng/ml/hr	16.0	26.1
ALDOSTERONE EXCRETION mg/24 Hr	16.8	21.3
SECRETION mg/24 Hr	137	140
PLASMA K^+ mEq/L	2.1	1.8
BLOOD PRESSURE	114/60	94/80
GFR	120	60

From Ref. 28

Aldosterone Sensitive Exchange Site

Pseudohypoaldosteronism of Infants

Cheek and Perry described a three month old male infant who lost weight after birth and was "dehydrated". The infant responded to the administration of sodium chloride loads and dexoxycorticosterone acetate (DOCA). Subsequently, when salt loading was withdrawn, DOCA was ineffective and it was concluded that the infant was not responding to DOCA. Subsequently, reports by Raine and Donnell (see accompanying figure) demonstrated continued excretion of sodium in the urine on a 1 mEq sodium intake during which time the infant's condition deteriorated and hyponatremia developed. This condition was often transitory.



Changes in urinary and serum sodium and potassium concentrations with reduction of sodium intake.

From Ref. 33

Raine summarized the cases reported (see accompanying table). In a recent paper by Rosler, this same syndrome was described in seven patients. High plasma aldosterone and renin activity were found in each of these subjects. Hyperkalemia was present in six of seven. There was no evidence of an adrenogenital defect in any of the infants studied. All had evidence of acute dehydration and a failure to gain weight. These patients did respond to 9-α-fluorohydrocortisone so that in contrast to the patients mentioned above who were unresponsive to mineralocorticoid, these infants may have had a partial defect. The aldosterone concentrations were not as high as found in some of the infants described earlier and it may be that the adrenal gland in these infants was not as responsive to angiotensin as some of the earlier cases.

31. Cheek DB and Perry JW: A Salt Wasting Syndrome in Infancy. Arch Dis Childh 33:252, 1958

32. Raine DN: A Salt-Losing Syndrome in Infancy. Arch Dis Childh 37:548, 1962

33. Donnell GN, Litman N and Roldan M: Pseudohypo-Adrenalocorticism. Am J Dis Child 97:65, 1959

34. Rosler A, Theodor R, Gazit E et al: Salt Wastage, Raised Plasma-Renin Activity, and Normal or High Plasma-Aldosterone: A Form of Pseudo-Hypoaldosteronism. Lancet 1(810):959, 1973

Authors	Cheek and Perry 1958	Donnell *et al* 1959	Lelong *et al* 1960	This Case
Sex	male	male	male	male
Race		caucasian	caucasian	caucasian
Age of Presentation (wks)	12	28	15	3
Presenting Symptoms	poor feeding & wt. gain cyanotic attacks	poor feeding & wt. gain, occas vomiting; eczematous rash	poor feeding & wt. gain. occas. vomiting	poor feeding & wt. gain. occas. vomiting napkin rash
Position in Family	First child	Fifth child	First child	Seventh child
Pregnancy	Pre-eclamptic toxaemia	Normal	Normal	Normal
Delivery	Induced, 2 wk prem.	Normal	Normal	Normal
Birth Wt. (lb)	5½	8	6½	7
Consanguinity		Absent	Absent	Absent
Family history	None	None	Possibly Mother	Possibly Sister
Subsequent Growth (wt.)		10 percentile at 3 years	3 percentile at 10 mos. 50 percentile at 2 yrs	3 percentile at 1½ yrs
Response to DOCA	None	None	None	None
Response to A.C.T.H.	Normal	Normal	Normal	Normal
Effect of NaCl on aldosterone excretion		Normal	Normal	
NaCl supplement/day	3 g. at 4 mos 5 g. at 6 mos	5 g. at 10 mos	4 g. at 6 mos	6 g. at 1 mo 8 g. at 3 mos
NaCl discontinued		14½ mos	2 yrs	15 mos

From Ref. 32

Primary Salt Wasting with Distorted Renal Architecture

While Thorn is generally credited with the first description of salt wastage occurring in the face of chronic kidney disease, an earlier paper by Peters examining the etiology of hypochloremia in nephritis found negative chloride balances in patients on a chloride restricted intake. The first of Thorn's cases was that of a 21 year old man who presented in 1938 for evaluation of nausea, weakness and vertigo. At the time of evaluation he had a recent weight loss, blood pressure of 64/46 and a urine that Thorn emphasized contained "no albumin or formed elements". Blood urea nitrogen was 96. The patient responded to the administration of glucose and saline solutions, but on another occasion became hypotensive with symptoms and again was placed on a large sodium chloride intake and had a dramatic clinical improvement. This clinical improvement was maintained on salt supplements alone and a previously administered adrenocortical extract was found to be unnecessary as was the administration of desoxycorticosterone. Subsequent pathological examination of his kidney revealed small kidneys with cysts throughout both renal masses, but no cysts in other organs. This tissue was subsequently reviewed by Strauss who felt that it was compatible with the diagnosis of medullary cystic disease. The second case of Thorn was a 21 year old woman who presented in shock and responded to the administration of saline solutions. At the time of discharge, the patient's blood pressure had increased and the blood urea nitrogen had fallen from 195 to 90. The patient subsequently died and an autopsy had evidence of pyelonephritis. This paper emphasized the problem in differentiation from an Addisonian crisis. Not only was hypotension present in the salt wasting state, but in addition, hyperkalemia and acidosis were a frequent accompaniment. Further, the patient with chronic kidney disease had a pigmented appearance frequently a bronzing which could be confused with the pigmentation seen in Addison's disease. Borst described a patient with polycystic kidney disease. Borst, in amazement, related "remarkable characteristic of these kidneys to excrete the urine, water and salt even when large amounts were given, 10 to 12 liters of water daily or more than 60 to 100 grams of salt per day, in spite of kidney function of only 8 to 10% and in spite of very low concentrations of sodium and chloride in the serum".

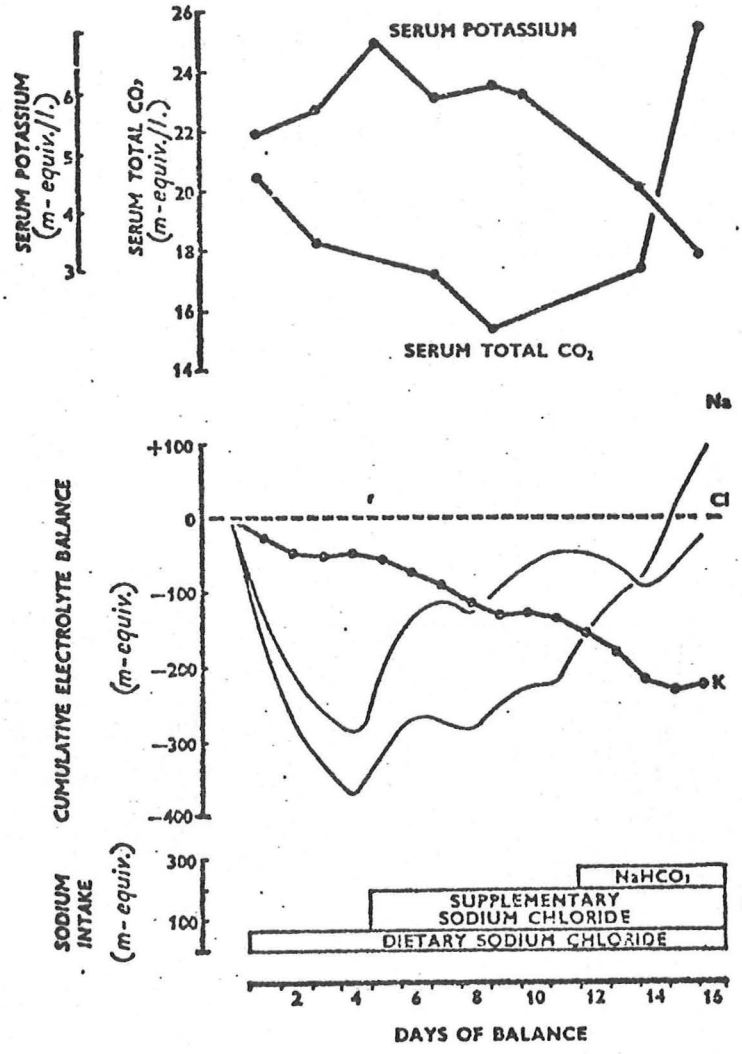
Enticknap reviewed the pathological findings in the patients described with salt wasting through 1952 and related that 10 of the 12 kidneys described had been contracted and multiple cysts were present.in two. While the glomeruli were invariably affected, in none were there evidence of active glomerulonephritis seen. The primary abnormalities were those of tubular and interstitial disease. Murphy pointed out that all patients did not present with "advanced Addison's disease". One of Murphy's cases had significant proteinuria and was felt to represent a case of chronic glomerulonephritis. The accompanying Table demonstrates the findings in Murphy's case consistent with salt wastage. Another of his cases was that of a patient ingesting excessive amounts of alkali. Stanbury and Mahler in an elaborate paper described a 32 year old woman with undiagnosed kidney disease who presented in a volume contracted state and responded to the administration of salt. She had the so-called bronze skin described by others. The accompanying figure demonstrates that on her usual dietary intake progressive salt depletion developed with a negative cumulative balance reaching almost 400 mEq. Only when supplements of sodium chloride were added did the salt balance reverse. At the same time that salt wastage was occurring the blood urea increased from 150 to 300 Mg/100 ml and subsequently

FEATURES OF SALT LOSING NEPHRITIS
H.H. (35 year old white male)

Date	Blood				Urine			B.P.	Comments
	Na mEq/L	Cl mEq/L	NPN	CO_2	S.G.	Volume	Cl mEq/L		
8-29-49	138.0	99.0	143.0	24.5	1.005	2400	—	140/100	Chronic glomerulonephritis. Alb. 1-2+. No casts.
1949-1951	—	—	163.0	26.0	1.008	1800	—	120/92	Studied at other institutions. Above diagnosis confirmed. Alb. 1-2+. No casts.
10-22-51	122.0	80.0	150.0	22.5	1.006	2200	—	120/80	Alb. 1+. No casts. Weak, pain in the legs, nausea. Diagnosis: Salt depletion.
12-18-51	118.0	86.0	187.0	30.5	1.004	1200	248.0	90/50	Muscle cramps in legs almost unbearable. Impending uremia. Muttering, delirium, state of collapse. Diagnosis: salt losing nephritis. 10 gm. sodium chloride and 10 gm. sodium bicarbonate orally.
2-26-52	135.0	98.0	70.0	32.0	1.006	1200-2500	262.0	130/90	Comfortable. Ambulatory and apparently normal.
9-20-52	142.0	102.0	68.0	33.0	1.008	—	—	136/100	Comfortable but not working.

From Ref. 40

CUMULATIVE EXTERNAL BALANCES OF SODIUM, CHLORIDE, AND POTASSIUM



From Ref. 41

declined with the administration of sodium chloride. Of some interest, the urine to plasma sodium ratio remained fixed despite wide swings in sodium balance. Compatible with the view that the kidney excreted a fixed concentration of sodium into the urine indifferent to the volume state of the individual. Aldosterone was measured in this patient and found to be ten times that of normal during the period of sodium depletion. The patient did develop hyperkalemia in a volume contracted state and this was attributed to the concurrent development of acidosis. Karetzky described a patient with pyelonephritis and periarteritis nodosa who had a salt losing state. It would appear that the salt wastage was secondary to the pyelonephritis and not the periarteritis nodosa.

35. Thorn G.W., Koepf GF and Clinton M Jr: Renal Failure Simulating Adrenocortical Insufficiency. N Eng J Med 231:76, 1944

36. Peters JP, Wakeman AM and Lee C: Total Acid-Base Equilibrium of Plasma in Health and Disease. J Clin Invest 6:551, 1929

37. Strauss MB: Clinical and Pathological Aspects of Cystic Disease of the Renal Medulla. Ann Intern Med 57:373, 1962

38. Borst JR: Disturbances in Water- and Salt Metabolism in the Final Stage of Chronic Renal Insufficiency. Acta Med Scand 136:1, 1949

39. Enticknap JB: The Condition of the Kidneys in Salt-Losing Nephritis. Lancet 2:458, 1952

40. Murphy FD, Settimi AL and Kozokoff NJ: Renal Disease with the Salt Losing Syndrome: A Report of Four Cases of So-Called "Salt Losing Nephritis". Ann Intern Med 38:1160, 1953

41. Stanbury SW and Mahler RF: Salt-Wasting Renal Disease. Quart J Med 28:425, 1959.

42. Karetzky MS: Periarteritis Nodosa Associated with Salt-Losing Nephritis. NYS J Med 69:1329, 1969

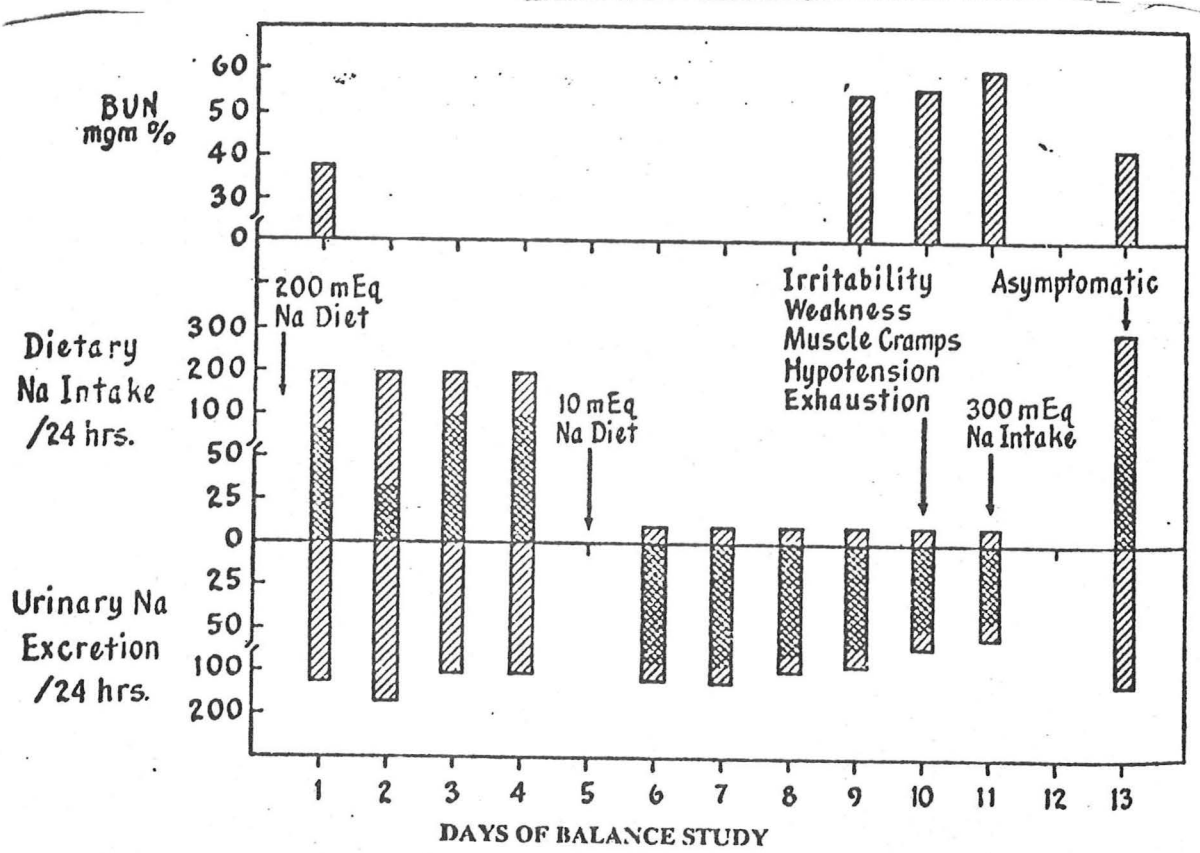
The late Maurice Strauss describing medullary cystic disease evaluated Thorn's original case and in addition added 17 other cases. The accompanying table from his article emphasizes that salt wastage was predominant in five cases, definitely present in 10 other and probably present in another. The cysts in this disease were present lying along the cortical medullary junction. The cortex was thin and demarcated and contained many hyalinized glomeruli.

Clinical Aspects of Medullary Cystic Disease in 18 Patients

Age	8 to 56 years; average 27 years; 14 under 34 years
Sex	12 male; 6 female
Hemoglobin	4.4 to 11.5 g/100 ml; average 8 g
Salt-wasting	Predominant in 5; present in 10; probably present in 1
Polyuria and nocturia	Present in 7; unknown or not recorded in 10
Urinary concentration	Generally below 1.010
Proteinuria	Absent or minimal early; 1+ to 3+ late
Cylindruria	Absent
White or red blood cells	Rare
Bacteriuria	Absent unless instrumented
Blood non-protein nitrogen	62 to 285 mg/100 ml; maximal pre-terminal 380 mg
Serum calcium	4.7 to 10.9 mg/100 ml; average 7.2 mg
Serum phosphorus	6 to 23 mg/100 ml; average 10 mg
Bone disease	Common in younger patients
Arterial blood pressure	Normal in 14; moderately elevated later in 6 of these
Family history of renal disease	Absent in 16

From Ref. 37

Franklin and Merrill refer to the presence of salt wasting occurring almost entirely in patients with "polycystic disease, hydronephrosis and pyelonephritis". Further, they pointed out that the salt wasting did not correlate with a decreased glomerular filtration nor an elevation in BUN but rather occurred at all levels of renal function. The association of interstitial nephritis both from analgesic abuse and from milk alkali syndrome have also been described. Ansari and Vennes found that 7 out of 50 patients with a milk alkali syndrome that have been described had a salt losing nephropathy. A patient which they have studied is illustrated in the accompanying table and shows that after approximately 10 days of salt restriction, the patient developed signs of salt wastage including irritability, weakness, muscle cramps, hypotension, and exhaustion. These symptoms were reverted by the administration of salt.



From Ref. 45

Other reports of milk alkali syndrome leading to salt wastage include that by Cheyne and Frank. Kahn and Levitt describe two patients with multiple myeloma who had evidence of salt wastage, both requiring more than 10 gm of sodium to maintain the patients in electrolyte and volume balance. The predominant pathologic finding in the one patient who was examined was that of marked tubular destruction and peritubular fibrosis associated with relatively normal appearing glomeruli. Lassen described an interesting patient with a documented hypernephroma who excreted most of his sodium from the right kidney, a kidney in which a very large hypernephroma was present. While volume contraction as a result of this phenomenon was not clearly documented it was necessary according to the author to administer large amounts of sodium to keep the patient in a satisfactory state of volume. Finally, Walker and Firminger described two siblings who presented with evidence of "dehydration". In both infants it was necessary to administer large amounts of sodium chloride to correct the state of "dehydration". The dehydration was associated with an elevated BUN and a reduced creatinine clearance. While the kidneys were grossly normal at autopsy in both subjects the glomeruli looked like newborn glomeruli and "distorted degenerating proximal convoluted tubules that had densely eosinophilic granular cytoplasms and irregular cortex were described. In some tubules, the epithelium was necrotic and sloughed into the lumen."

43. Strauss MB: See Ref.37

44. Franklin SS and Merrill JP: The Kidney in Health; The Nephron in Disease. Am J Med 28:1, 1960

45. Ansari A and Vennes JA: Chronic Milk-Alkali Syndrome and Salt-Losing Nephropathy. Minn Med 54:611, 1971

46. Cheyne AI and Whitehead TP: Thorn's Syndrome Following Excessive Ingestion of Alkalis. Lancet 1:550, 1954

47. Frank A and Greenspan G: Milk-Alkali Syndrome Complicated by Salt-Losing Nephritis. N Eng J Med 260:210, 1969

48. Kahn T and Levitt MF: Salt Wasting in Myeloma. Arch Intern Med 126:664, 1970

49. Lassen UV and Sagild U: Salt-Losing Syndrome Due to Unilateral Renal Disease (Hypernephroma). Acta Med Scand 168:65, 1960

50. Walker SH and Firminger HI: Familial Renal Dysplasia with Sodium Wasting and Hypokalemic Alkalosis. Am J Dis Child 127:882, 1974

Mechanisms of Salt Wasting Kidney Disease

The wastage of sodium in chronic renal disease in the earlier section was listed as specific anatomical diagnoses. Landis and subsequently Nickel described in patients with non-specific chronic renal insufficiency that salt restriction led to a decrease in renal function. The accompanying table from Nickel shows that during a period of sodium deprivation the urinary excretion of sodium continued in contrast to subjects with normal renal function. In addition, in most cases there was a substantial decrease in the clearance of inulin and clearance of PAH with sodium deprivation. In 1966, papers by Coleman et al and Gonick et al demonstrated that salt wastage of a mild degree occurred in patients with tubular disease but not with glomerular disease. The accompanying graphs from Gonick's paper shows that patients with tubular disease had a larger fractional sodium excretion than did those with glomerular disease and that a particular patient with chronic pyelonephritis (JJ) continued to excrete sodium in excess of intake on a low salt diet. Coleman et al, who studied a group of patients with a variety of forms of interstitial disease but none with glomerulonephritis found the patients continued to waste salt on a low grade basis when salt intake was markedly reduced as illustrated in the accompanying figure from their paper of one of the representative studies performed. Further, they made the important observation that when a water load was given the salt wasting state was exaggerated. This was due to the fact that the concentration of sodium in the urine remained the same, but the urine volume increased. These authors felt that this was the result of the water load resulting in the delivery of more salt to some distal part of the nephron which is then swept out into the urine implying a form of a distal defect. The continued increased concentration of sodium in the urine despite evidence of vascular collapse was unresponsive to large doses of 9-α-fluorohydrocortisone. The authors also observed that when the glomerular filtration rate was lowered by the administration of a vasodilator, salt wasting was diminished. Finally, when normal subjects were given mannitol in an osmotic load comparable to that of the patients with renal failure the same flow dependence of sodium excretion was found to a water load. The large osmotic load per nephron appears to be an important factor in perpetuating sodium excretion.

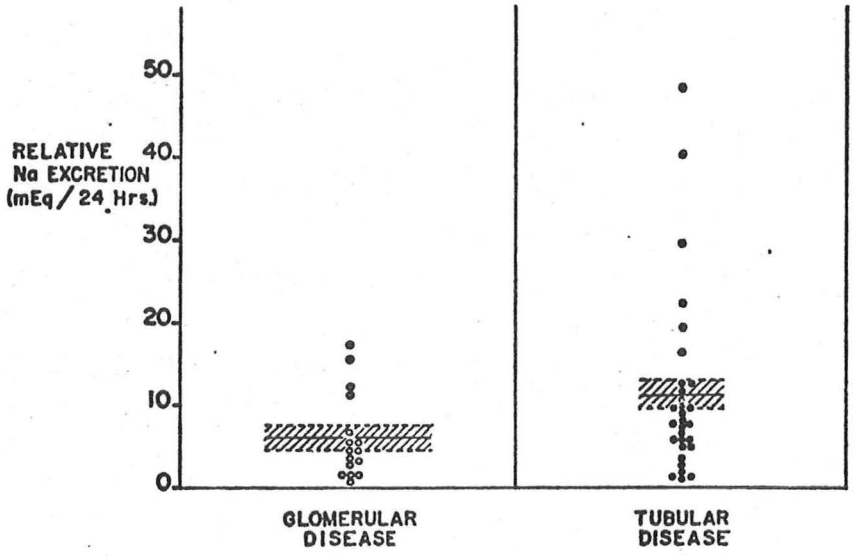
THE EFFECT OF SODIUM DEPRIVATION ON BODY WEIGHT, RENAL FUNCTION, URINARY SODIUM AND POTASSIUM EXCRETION, AND ON PLASMA ELECTROLYTES

Patient Diagnosis Sex Age S.A	Regimen*	Body wt.	C_{in}	C_{pah}	Na	BUN	U_{NaV}
		$m.^2$	Kg	ml/min	ml/min	mEq/L		µEq/min
			Normal Renal Status					
A.C.								
Rheum.arthritis	Control	43.6	105	755	137	10	203.6
F 37 1.49	Na depriv.	42.8	105	550	134	11	5.8
A.B.								
Pulm.emphysema	Na depriv.	64.7	120	505	137	15	1.2
M 45 1.70	Repletion	66.2	125	575	140	13	27.3
			Chronic Renal Insufficiency				
G.B.								
Malig.neph.scl.	Control	62.6	30	100	132	32	48.7
M 21 1.86	Na depriv.	62.5	15	60	132	30	17.5
M.B.								
Malig.neph.scl.	Control	68.5	12	50	136	77	205.3
M 28 1.91	Na depriv.	67.5	7	25	132	102	149.3
C.P.	Control	82.0	7	25	135	66	165.6
Polycystic disease	Na depriv.	81.2	8	15	136	64	162.3
F 57 1.87	Repletion	84.0	12	25	142	60	319.5
J.F.	Control	50.2	20	105	134	44	166.9
Chronic glom.neph.	Na depriv.	48.6	12	95	131	63	33.7
M 56 1.47	Repletion	51.4	26	125	136	37	277.0
T.C.	Control	61.6	50	250	138	40	129.0
Chronic glom.neph.	Na depriv.	60.8	30	230	137	65	41.6
M 54 1.70	Repletion	60.9	45	295	140	38	264.2

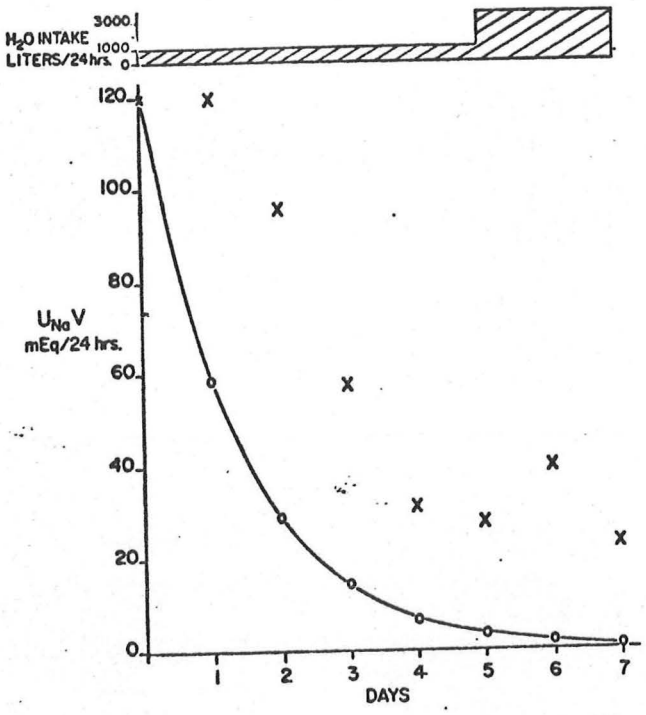
*Regimen: Control, on diet containing 70 to 105 mEq. sodium daily, at least 1 gm. protein per Kg. daily, and adequate caloric provision; Na depriv., sodium intake reduced to 18 to 25 mEq daily, and cation exchange resin (Carbo-resin) 60 gm daily in divided doses; Repletion, control diet and supplement of 85 mEq. sodium daily. Each study at termination of a period of at least 5 days under each regimen.

All values for renal clearances and urinary sodium are averages of three determinations.

From Ref. 52

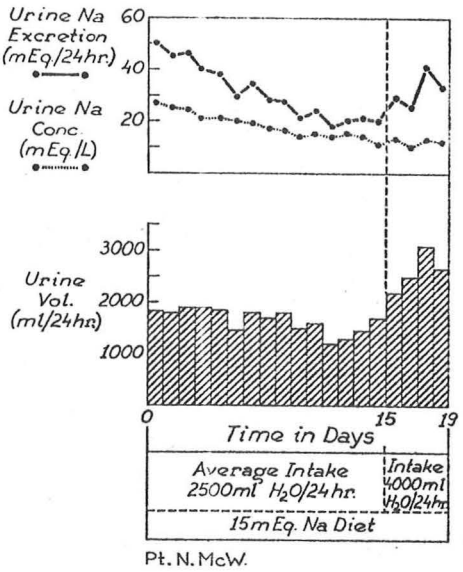


Comparison of 'relative' sodium excretion in patients with glomerular diseases and patients with tubular diseases. Mean and standard error for each group are represented by the horizontal line and shaded area, respectively. 'Relative' sodium excretion ($U_{Na}V \times GFR/100$) corrects sodium excretion to a normal solute load per nephron.



Daily sodium excretion in patient J. J. after initiation of a 200 mg sodium diet. Values obtained from patient J. J. are designated by an 'X' values predicted for a normal subject by an 'O'.

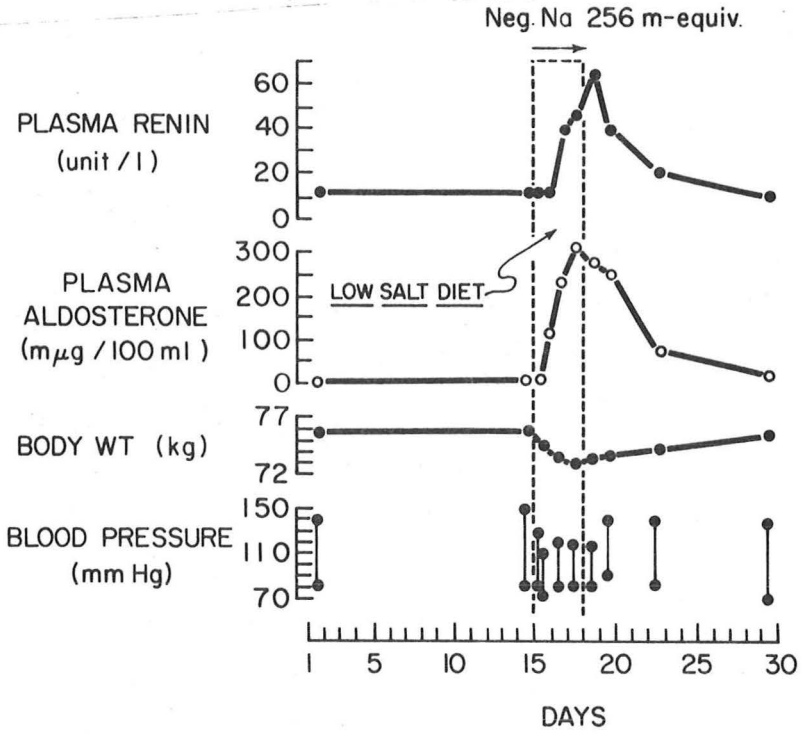
From Ref. 53



EFFECT OF INCREASING THE WATER INTAKE DURING SALT RESTRICTION ON URINARY CONCENTRATION AND EXCRETION OF SODIUM IN A PATIENT WITH CHRONIC RENAL DISEASE.

From Ref. 54

Continued excretion of sodium in these subjects does not appear to be due to aldosterone deficiency. As indicated earlier, the paper of Coleman showed no effect of 9-α-fluorohydrocortisone. Fraser in the study of a patient with salt wasting renal disease, as shown on the accompanying figure, found that on a low salt diet there was a substantial increase in plasma aldosterone and renin. Nonetheless the patient's blood pressure fell and a mild degree of salt wastage occurred. Other studies by Walker of patients with chronic renal failure subsequently on hemodialysis found that the aldosterone axis is intact. Popovitzer also was unable to demonstrate any evidence of reduced aldosterone in a patient with chronic renal disease and salt wastage. This patient also had hyperkalemia which could only be attributed to decreased glomerular filtration rate. On the other hand, Gerstein describes a patient who, on a reduced sodium diet, wasted salt which was corrected by the administration of large doses of 9-α-fluorohydrocortisone. In addition, during the time of salt restriction without 9-α-fluorohydrocortisone he developed hyperkalemia which reverted with the administration of mineralocorticoid suggesting a mild aldosterone responsive defect occurred.



From Ref. 56

51. Landis EM, Elsom KA, Bott PA et al: Observations on Sodium Chloride Restriction and Urea Clearance in Renal Insufficiency. J Clin Invest 16:525, 1935

52. Nickel JF, Lowrance PB, Leifer E et al: Renal Function, Electrolyte Excretion and Body Fluids in Patients with Chronic Renal Insufficiency Before and after Sodium Deprivation. J Clin Invest 32:68, 1953

53. Gonick HC, Maxwell MH, Rubini ME et al: Functional Impairment in Chronic Renal Disease. I. Studies of Sodium-Conserving Ability. Nephron 3:137, 1966

54. Coleman AJ, Arias M, Carter NW et al: The Mechanism of Salt Wastage in Chronic Renal Disease. J Clin Invest 45:1116, 1966

55. Gerstein AR, Kleeman CR, Gold EM et al: Aldosterone Deficiency in Chronic Renal Failure. Nephron 5:90, 1968

56. Fraser R, James VHT, Brown JJ et al: Changes in Plasma Aldosterone, Cortison, Corticosterone, and Renin Concentration in a Patient with Sodium-Losing Renal Disease. J Endocr 35:311, 1966

57. Popovtzer MM, Katz FH, Pinggera WF et al: Hyperkalemia in Salt-Wasting Nephropathy. Arch Intern Med 132:203, 1973

Kahn, in a study of 39 patients with a variety of forms of renal insufficiency found that after these subjects had come into salt balance and were studied by water loading techniques that the excretion of sodium was related to the excretion of nonelectrolyte solute in the urine. This nonelectrolyte solute was determined by subtracting from the urine osmolality the product of two times the urine sodium plus potassium concentration. When mannitol was administered to subjects with a low glomerular filtration rate, an increase in fractional sodium excretion was greater than in those subjects who initially had a higher glomerular filtration rate (see accompanying figure).

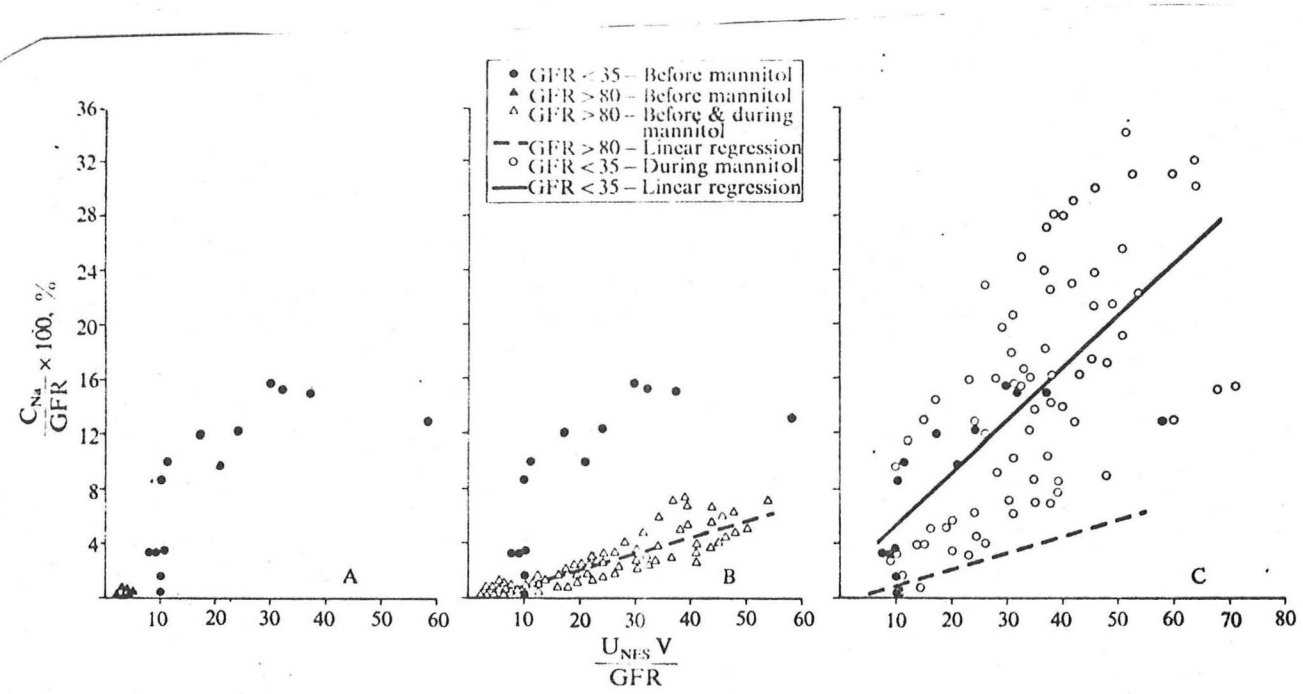


Fig. 3. *Fractional sodium excretion versus nonelectrolyte solute excretion per GFR ($U_{NES}V/GFR$).* (A) Data obtained from subjects in the high (▲) and low (●) C_{Na}/GFR group at maximal water hydration prior to mannitol loading. (B) Data obtained in subjects in the high GFR group prior to and during mannitol loading (△), compared to points obtained in the low GFR group after water hydration alone (●). The mean regression line for all the points in the high GFR group is depicted (- - -). (C) Data obtained from subjects in the low GFR group prior to (●) and during mannitol loading (○). The mean regression line for the low (——) and the high (- - -) GFR groups are given.

From Ref. 58

In addition, these authors felt that the fraction of the filtered sodium reaching the distal tubule was greater in subjects with a low GFR based on C_{H_2O} observations. However, when the non-electrolyte solute excretion was increased in the high GFR group, the index of fractional distal tubular sodium load remained lower than most of the levels noted prior to mannitol loading in the low GFR group. The authors felt that this made it unlikely that the higher non-electrolyte solute excretion per GFR could be the sole factor responsible for the higher fractional distal sodium load noted in the low GFR group prior to mannitol loading. It would therefore seem that the overall the overall tubular reabsorption for sodium in the proximal tubule of subjects with chronic renal disease is more susceptible to the inhibition at the outset prior to the administration of an osmotic load. Possible explanations for reduced fractional sodium reabsorption in chronic renal disease may include (1) a increase in single nephron GFR, (2) an augmentation of sodium excretion which may be flow dependent and is a result of increased urine flow per nephron. This latter finding is supported by the prior data of Coleman, (3) and finally it seems unlikely that a deficiency of aldosterone was present in these studies because some of the subjects were treated with mineralocorticoid prior to these experimental manipulations and their results were no different than those who did not receive such treatment.

58. Kahn T, Mohammad G and Stein RM: Alterations in renal tubular sodium and water reabsorption in chronic renal disease in man. Kidney Intern 2:164, 1972

59. Coleman AJ: See Reference 54

The Role of Natriuretic Factor

The role of natriuretic factor has been postulated for years to explain the increased fractional sodium excretion found in patients with chronic renal insufficiency. This increased fraction of the filtered sodium excreted in the urine is of course necessary in order to permit the subjects with chronic renal disease to excrete their dietary sodium loads. Bricker's group has been the most successful in recent years in developing an assay for natriuretic factor and in applying it to patients with chronic kidney disease. Their studies indicate that this substance is present in uremic subjects with a high fractional excretion of sodium but not in uremic nephrotic patients who are retaining salt. Another investigator from Bricker's laboratory, Schmidt, has found that the adaptation to chronic renal disease, that is the increase in the fractional excretion of sodium can be prevented if the dietary intake of sodium is reduced commensurate with the decrease in glomerular filtration rate. Further, in these uremic dogs in whom renal mass and glomerular filtration rate had been reduced natriuretic activity was found in the uremic dogs who were continued on a constant salt intake and had a high fractional sodium excretion but was not found in those animals where the salt intake had been proportionately reduced with the decrease in renal mass and glomerular filtration rate. This adds further support to the potential role of natriuretic hormone in promoting increased sodium excretion in chronic renal disease.

60. Bricker NS, Schmidt RW, Weber H et al: The Modulation of Na Excretion in Chronic Renal Disease. The Possible Role of a Natriuretic Hormone in Modern Diuretic Therapy. The Treatment of Cardiovascular and Renal Disease, London, Excerpta Medica Foundation, Amsterdam 40, May 1972

61. Bourgoignie JJ, Hwang KH, Ipakchi E et al: The Presence of a Natriuretic Factor in Urine of Patients with Chronic Uremia. J Clin Invest 53:1559, 1974

62. Bourgoignie JJ, Hwang KH, Espinel C et al: A Natriuretic Factor in the Serum of Patients with Chronic Uremia. J Clin Invest 51:1514, 1972

63. Schmidt RW, Bourgoignie JJ and Bricker NS: On the Adaptation in Sodium Excretion in Chronic Uremia. The Effects of "Proportional Reduction" of Sodium Intake. J Clin Invest 53:1736, 1974

B. Secondary Causes of Renal Salt Wasting

Addison's Disease

Thomas Addison described in his treatise on the constitutional and local effects of "Disease of the Supra-renal Capsules" a 26 year old carpenter who among other things had the following complaints, "for the last month he had discontinued work on account of attacks of giddiness and dimness of sight, accompanied by peculiar pain at the back of the head and partial loss of consciousness. These attacks would occur several times in the course of the day, upon any unusual exertion, always while in the standing posture, and were instantly relieved by sitting or lying down. Since he has discontinued his employment they have only occurred on getting out of bed in the morning." In a subsequent part of the report, he described the pathological appearance of the adrenal glands of this man and states "each supra-renal capsule was completely destroyed and converted into a mass of strumous disease, the latter of all degrees of consistency." The role of the absence of mineralocorticoid, resulting in salt wastage was most clearly identified by Roemmelt where with mineralocorticoid deficiency approximately 2% of the sodium filtered at the glomerulus appeared in the urine. The following table taken from a paper by Liberman illustrates in a case of partial surgical adrenal insufficiency the effect of a low salt diet resulting in salt wastage and by the end of the salt deprivation period symptoms of hypovolemia. This case has far less than 2% of the filtered sodium appearing in the urine and is representative of a patient in whom some mineralocorticoid activity is present.

Effect of a low sodium diet
on an adrenalectomized patient (E.J.L.)

Day	Body wt.	Diet Na	Diet K	Urine Na	Urine K	Serum Na	Serum K
	(kg)	(mEq/day)		(mEq/day)		(mEq/l)	
1	51.2	150	50	215.8	73.8		
2	51.1	150	50	128.6	65.4		
3	51.0	150	50	136.9	61.0		
4	51.1	150	50	163.4	76.3	139.5	4.30
5	50.5	10	50	65.3	51.8		
6	50.5	10	50	39.7	32.4		
7	50.1	10	50	40.4	27.0	136.0	4.97
8	49.9	10	50	33.2	25.0		
9	49.4	10	50	26.2	21.6		
10	49.2	10	50	19.0	18.7		
11	48.8	10	50	28.2	23.5	129.5	5.70
12	48.4	10	50	30.2	13.5		
13	48.6	10	50	28.4	21.3		

From Ref. 66

In infancy, the manifestation of adrenocortical insufficiency is that of a salt losing syndrome. An afflicted infant will show signs of dehydration, poor feeding, failure to gain weight or actual weight loss, intermittent febrile episodes, and occasional vomiting. Blood will reveal hyponatremia, hyperkalemia and metabolic acidosis. Hyperpigmentation may or may not be seen. The accompanying table lists the causes of adrenal salt wasting in infancy.

These are to be distinguished from the patients described in an earlier section of tubular insensitivity to mineralocorticoid. These patients respond to the administration of exogenous mineralocorticoid.

ADRENOCORTICAL HYPOFUNCTION

(1) Adrenal Insufficiency Usually Seen in Infancy (salt-losing syndrome)

a. Defects in the biosynthesis of aldosterone

i. Transient?

ii. Permanent, as hereditary 'inborn error'

-- lipoid adrenal hyperplasia (20, 22 desmolase defect?)	with congenital adrenal hyperplasia
-- 3β-dehydrogenation defect	
-- 21-hydroxylation defect	
-- 18-oxidation defect (18-hydroxylation type; 18-dehydrogenation type)	without congenital adrenal hyperplasia

b. Haemorrhage and calcification in the adrenal glands.

c. Congenital adrenal hypoplasia of the adrenal glands.

d. 'Transient adrenocortical insufficiency in infancy (Jaudon, 1948)?'

From Ref. 67

64. Wilks S and Daldy TM: A Collection of Published Writings of the Late Thomas Addison, M.D. New Sydenham Society, London, 1868. Pp. 209.

65. Roemmelt JC, Sartorius OW, and Pitts RF: Excretion and reabsorption of sodium and water in the adrenalectomized dog. Am J Physiol 159:214, 1949

66. Liberman B and Wajchenberg BL: Adaptation to Dietary Sodium Restriction in Adrenocortical Insufficiency. Rev Franc Etudes Clin Et Biol 14:46, 1969

67. Visser HKA: The Adrenal Cortex in Childhood, Part 2: Pathological Aspects. Arch Dis Childh 41:113, 1966

68. Oetliker OH and Zurbrugg RP: Renal Tubular Acidosis in Salt-Losing Syndrome of Congenital Adrenal Hyperplasia (CAH). J Clin Endocr 31:447, 1970.

69. David R, Golan S, and Drucker W: Familial Aldosterone Deficiency: Enzyme Defect, Diagnosis, and Clinical Course. Pediatr 41:403, 1968

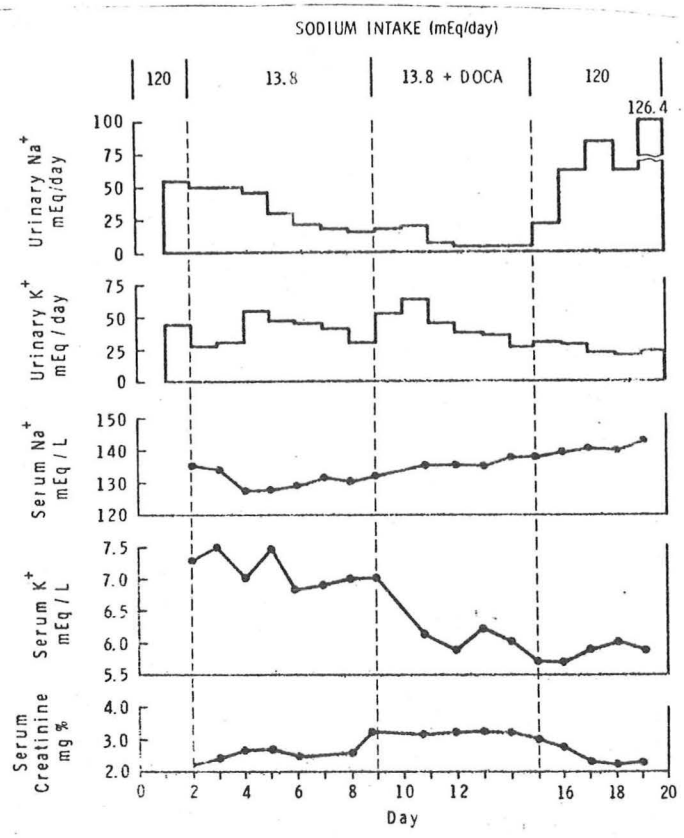
70. Rappaport R, Dray F, Legrand JC et al: Hypoaldosteronisme congenital familial par defaut de la 18-OH-dehydrogenase. Pediat Res 2:456, 1968

A paper by Comacho described an eight month old pseudohermaphrodite male with salt wasting whose steroid excretion data suggested a deficiency of pregnenolone synthesis with bilateral adrenal cortical hyperplasia.

Camacho AM, Kowarski A, Migeon CJ et al: Congenital Adrenal Hyperplasia Due to a Deficiency of One of the Enzymes Involved in the Biosynthesis of Pregnenolone. J Clin Endocr 28:153, 1968

Hypoaldosteronism

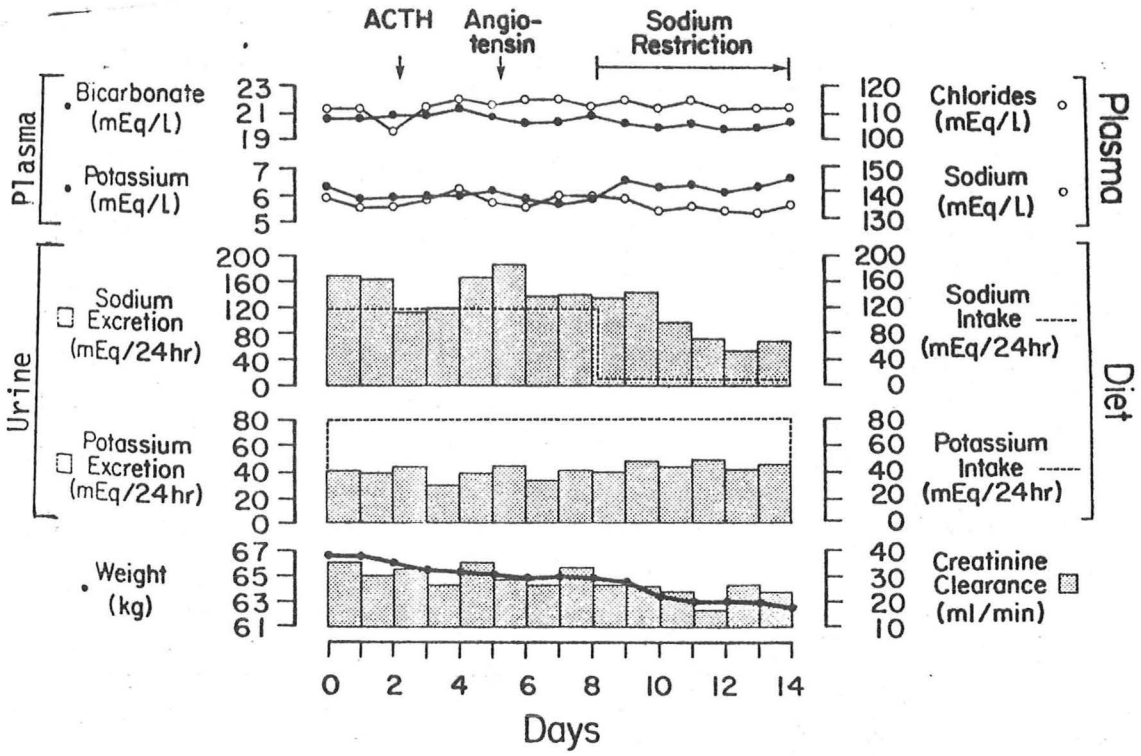
In the adult, a few cases of selective hypoaldosteronism with salt wasting have been described. Whether this is a uniform finding in all cases or not is not clear because some of the case reports have not described the response of these patients to severe salt restriction. These patients do continue to elaborate glucocorticoids and these steroids presumably have sufficient mineralocorticoid activity to prevent the development of the severe salt wasting state. Many of these cases were initially discovered because of the presence of persistent hyperkalemia. The accompanying figure is the best demonstration of salt wastage occurring in this setting. This was a 72 year old woman who initially presented with gout and was found to have persistent hyperkalemia. Thorough testing of her adrenocortical pituitary function was normal except for the production of aldosterone. Her aldosterone secretory rate was 7.5 micrograms in 24 hours. At a time when her plasma renin activity was 433 ng/100 ml. The infusion of angiotensin II only produced a slight increase in the aldosterone secretory rate. This patient's aldosterone secretion was increased into the normal range by the combined administration of a low salt diet and Aldactone. This was accomplished at the expense of considerable underperfusion with a rise of the serum creatinine from 1.5 to 2.5 mg%. This patient then seemed to have some responsiveness of the zone of glomeruloso to appropriate stimuli, but this was markedly attenuated and reduced so that on either a normal diet or a low salt diet alone, aldosterone production was diminished.



From Ref. 71

Three papers by Hudson, Wilson and Perez describing patients with hypoaldosteronism either demonstrate the persistent excretion of sodium on a low salt diet or suggest that salt wastage occurs. However, in no instance was the documentation of a decrease in organ perfusion associated with the continued excretion of salt. These cases are not clearly that of salt wastage.

The association of renal insufficiency, hyperkalemia, and salt wastage had been described by Gerstein and Weidmann. In the earlier section on salt wastage and renal failure, mineralocorticoid function was normal or salt wastage continued to occur in the face of administered exogenous mineralocorticoid. The accompanying figure taken from Case 2 of Weidmann shows the effect of salt restriction in a 75 year old man in whom hyperkalemia was found. The patient continued to elaborate sodium in excess of intake, lost weight and had a decrease in his creatinine clearance. In addition the patient had orthostatic hypotension. Weidmann also found that the plasma renin activity and aldosterone appeared to be depressed in these patients. The interpretation of this was based on a comparison between plasma renin activity of normal control subjects and those of the cases studied with varying salt excretions. This data is illustrated in Figure 4 from his paper. A problem in interpretation arises because the four subjects all had decreased renal function and increased fractional sodium excretion and may have had an appropriate plasma renin level considering their sodium excretion.



From Ref. 76

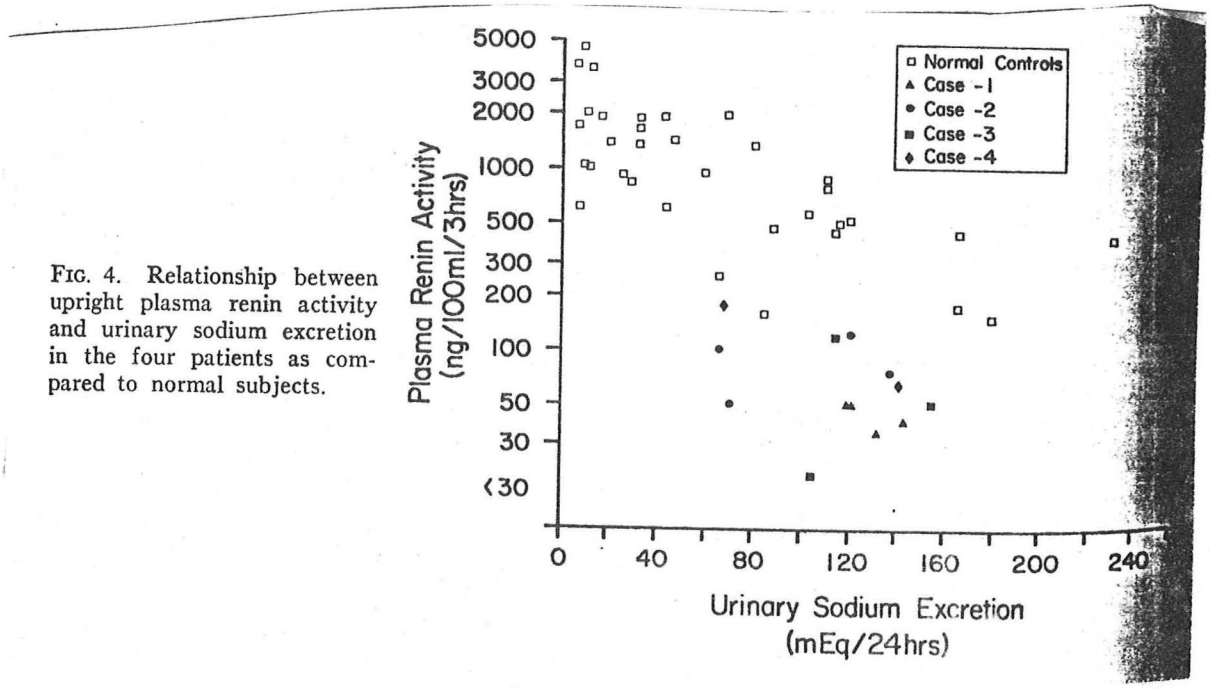


FIG. 4. Relationship between upright plasma renin activity and urinary sodium excretion in the four patients as compared to normal subjects.

From Ref. 76

71. McGiff JC, Muzzarelli RE, Duffy PA et al: Interrelationships of Renin and Aldosterone in a Patient with Hypoaldosteronism. Am J Med 48:247, 1970

72. Hudson JB, Chobanian AV, and Relman AS: Hypoaldosteronism. N Eng J Med 257:529. 1957

73. Wilson, ID and Goetz FC: Selective Hypoaldosteronism after Prolonged Heparin Administration Am J Med 36:635, 1964

74. Perez G, Siegel L and Schreiner GE: Selective Hypoaldosteronism with Hyperkalemia. Ann Intern Med 76:757, 1972

75. Gerstein AR: See Reference 55

76. Weidmann R, Reinhart R, Maxwell MH et al: Syndrome of Hyporeninemic Hypoaldosteronism Hyperkalemia in Renal Disease. J Clin Endocr Metab 36:965, 1973

Excess Natriuretic Hormone

The role of the natriuretic substance in the mechanism of the increased excretion of sodium filtered at the glomerulus in chronic renal disease was described in in an earlier section (page 25) This work in recent years in particular has been performed by Bricker. It is of substantial interest that Bricker mentions in the discussion of a paper he presented in London in May of 1972 in response to a question concerning the natriuretic substance in patients with uremia due to salt losing pyelonephritis that one patient studied whose glomerular filtration rate was 20 ml/min had the most positive assay for natriuretic activity of any patient they had investigated to that point. While most of the patients with salt wasting disease have adequate anatomical evidence to support that a destructive lesion of the renal architecture is the predominate mechanism resulting in salt wastage. This observation is fascinating and requires further confirmation. (Refer to Bricker, Pg 25 , Paragraph 2).)

A natriuresis has been described with a redistribution of blood volume and concomitant relative central hypervolemia, with atrial arrhythmias, and after emersion to the neck. While in none of these instances has a true salt wasting state been described, these studies have all been acute in type and suggest that the physiological mechanisms involved included suppression of the renin aldosterone system, suppression of antidiuretic hormone, and stimulation of a natriuretic substance. Should such a physiological derangement persist, the natriuresis could continue and then when the abnormal stimulus was relieved the individual would be left in a relatively salt depleted state. That such might be the case is suggested but not confirmed by the observation that deep-sea divers have a substantial diuresis while submerged and crave salt upon coming to the surface.

77. Bricker NS: See Reference 60.

78. Epstein M: unpublished communication

79. Epstein M, Pins DS and Miller M: Suppression of ADH during water immersion in normal man. J Appl Physiol 38:1038, 1975

Astronauts returning from sojourns in outer space have substantial orthostatic hypotension for one to two days after returning to a terrestrial existence. Accompanied with this is a two to twelve pound weight loss during flight, the observation that substantial sodium retention occurs during these first few days upon returning to earth and that their creatinine in the few instances when it has been checked has been elevated shortly after landing. This syndrome, of course, would be a relative salt wastage environmentally induced and only evidenced when the individual returned to the environment where stimuli for salt excretion were not present.

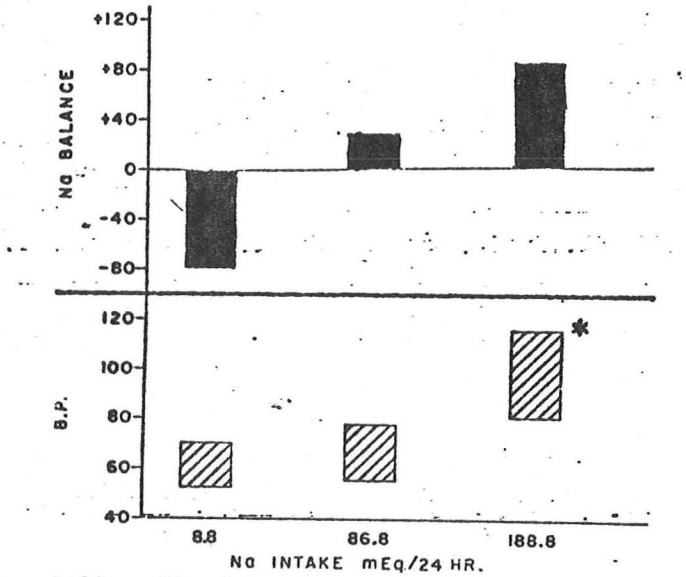
Berry, CA: Bioastronautics Data Book Second Edition, Parker and West, NASA, SP-3006, 1972, Pg 352

Neurogenic

Orthostatic hypotension The syndrome of primary (idiopathic) orthostatic hypotension has many features compatible with the salt wasting state. Whereas the astronaut has to radically alter his environment to waste salt, the patient with orthostatic hypotension only needs to assume the recumbent position to waste salt relative to his needs in the upright position. Wagner observed that the patient with orthostatic hypotension had a greatly exaggerated natriuretic response to the administration of both sodium and water when supine.

Shear documents the requirement for salt loading to maintain an adequate standing blood pressure as shown in the accompanying figure.

Total Three-Day Sodium Balances in Relation to Means of Standing Systolic and Diastolic Blood Pressures



*+0.3 mg. of fluorohydrocortisone acetate/day.

From Ref. 81

The amount of salt required in this circumstance can on occasion be extraordinary. The accompanying Table from two orthostatic patients that we have studied demonstrates that in the supine position when the blood pressure was normal a considerable degree of sodium excretion was occurring, but when the patient was put in an upright or semi-upright position sodium excretion greatly decreased as did the glomerular filtration rate and renal blood flow as measured by the clearance of para aminohippurate. In one subject, even though hypotensive, sodium excretion continued. In the other subject sodium excretion persisted but at a reduced rate.

ORTHOSTATIC HYPOTENSION

PATIENT	GFR		RENAL BLOOD FLOW		$U_{Na}V$		$U_{Cl}V$	
	ml/min		ml/min		μEq/min		μEq/min	
	S	U	S	U	S	U	S	U
1	80	40	448	62	169	6	217	7
2	84	75	549	285	1105	69	978	55

S = SUPINE
U = UPRIGHT

From Ref. 83

The mecanism for the continued excretion of sodium and the augmented response in the supine position include (1) a relative aldosterone deficiency, (2) normal or increased blood pressure in the supine position, (3) the potential for a disordered feedback suppression loop between the macula densa and the afferent arteriole of the glomerulus. Aldosterone deficiency or partial aldosterone responsiveness have been described by Botticelli and Slaton which probably results from lack of stimulation to the zone of glomeruloso of the adrenal cortex from angiotensin II. The lack of production of plasma renin appears to be associated with a defect in the efferent sympathatic pathway. Whereas those patients with the Holmes's-Adie syndrome where the afferent loop from the baroreceptor is involved seem to have increased plasma renin activity and no evidence of aldosterone deficiency.

An increased natriuresis in the hypertensive patient with the administration of saline is a well known phenomenon. Many of the patients with orthostatic hypotension are hypertensive in the supine position and in a sense may be responding to an autoinfusion of saline occurring as the consequence of redistribution of blood volume in the supine position leading to the exaggerated sodium diuresis. Then when the patient returns to the upright position, he is volume depleted.

The interrelationship of the macula densa to glomerular filtration rate by a intrarenal renin release mechanism has been the subject of recent investigation. Whether this mechanism is disordered or not in orthostatic hypotension is not clear but may be the explanation for the results found in a study of our patients who despite a marked fall in renal blood flow had a persistence of both glomerular filtration rate and sodium excretion at a time when their blood pressure was profoundly lowered by the effects of a semi-upright tilt.

80. Wagner HN Jr: Orthostatic Hypotension. Bull Johns Hopkins Hosp 105:322, 1959

81. Shear L: Renal Function and Sodium Metabolism in Idiopathic Orthostatic Hypotension. N Eng J Med 268:347, 1963

82. Shear L: Orthostatic Hypotension. Arch Intern Med 122:487, 1968

83. Fuller TJ, Parker TF, and White MG: unpublished observation

84. Botticelli JT, Lange RL and Kelly OA: Postural Hypotension with Decreased Central Blood Volume and Impaired Aldosterone Response. Am J Med 37: 147, 1964

85. Slaton PE and Biglieri EG: Reduced Aldosterone Excretion in Patients with Autonomic Insufficiency. J Clin Endocr Metab 27:37, 1967

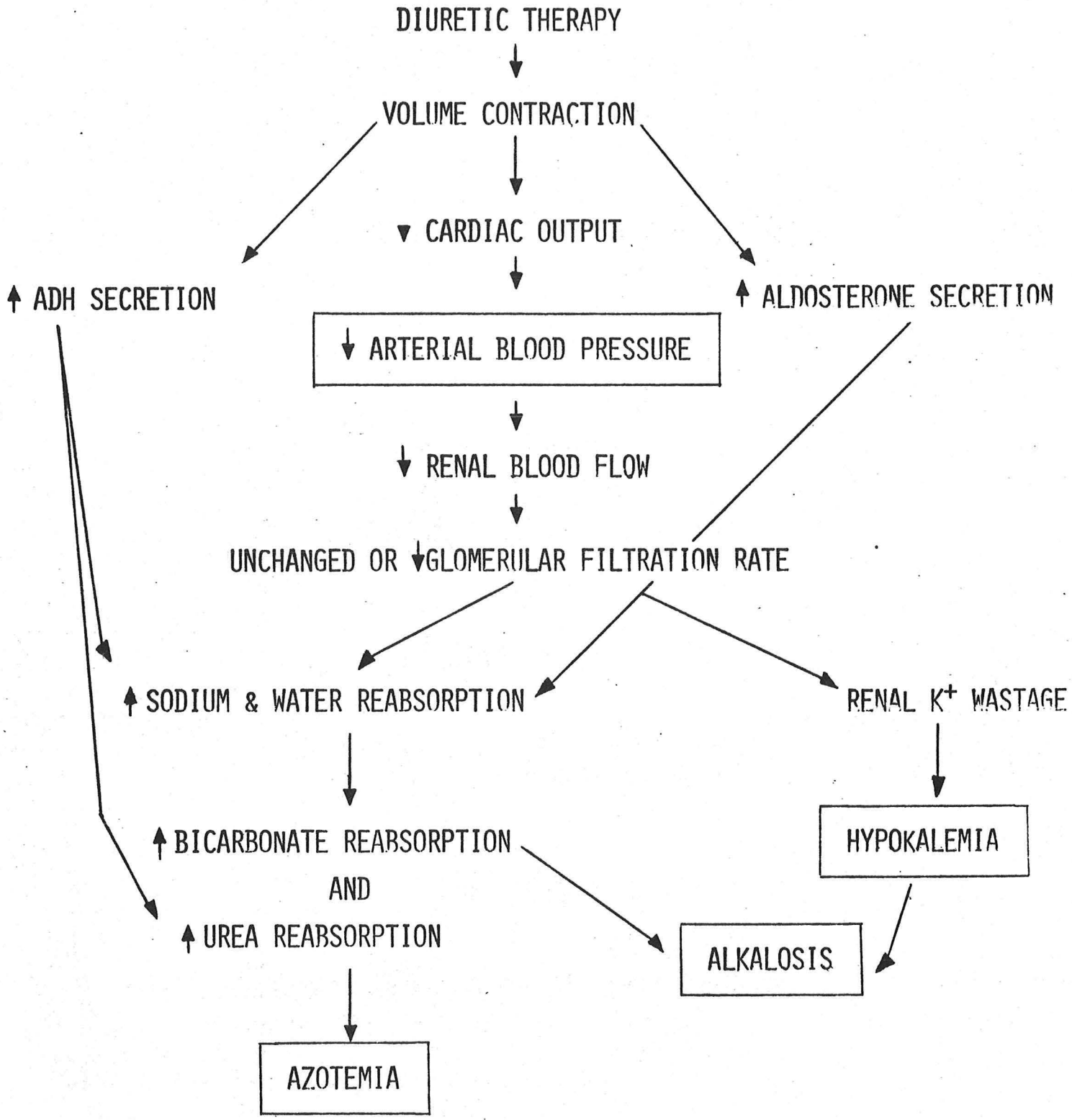
86. Gordon RD, Kuchel O, Liddle GW et al: Role of the sympathetic nervous system in regulating renin and aldosterone production in man. J Clin Invest 46:599, 1967

87. Love DR, Brown JJ, Chinn RH et al: Plasma Renin in Idiopathic Orthostatic Hypotension: Differential Response in Subjects with Probable Afferent and Efferent Autonomic Failure. Clin Sci 41:289, 1971

88. Schnermann J: Regulation of single nephron filtration rate by feedback - facts and theories. Clin Nephrol 3:75, 1975

Drug Induced

Diuretics While diuretics are usually prescribed to facilitate the excretion of excess salt and water, on occasion they may be inappropriately used and result in the development of a salt depleted state and continue to promote salt wastage. As indicated in the accompanying diagram, the effects of diuretics may include a reduction in the arterial blood volume with a fall in glomerular filtration rate, a tendency towards potassium wastage, and an increase in water reabsorption from ADH stimulation resulting in the development of hyponatremia. The diuretics which inhibit the reabsorption of chloride in the ascending limb of the loop of Henle can be particularly troublesome


DIURETIC THERAPY
VOLUME CONTRACTION
CARDIAC OUTPUT
ADH SECRETION
ALDOSTERONE SECRETION
ARTERIAL BLOOD PRESSURE
RENAL BLOOD FLOW
UNCHANGED OR GLOMERULAR FILTRATION RATE
SODIUM & WATER REABSORPTION
RENAL K+ WASTAGE
BICARBONATE REABSORPTION
AND
UREA REABSORPTION
HYPOKALEMIA
ALKALOSIS
AZOTEMIA

From Ref. 89

VOLUME DEPLETION THROUGH ILL-ADVISED USE OF DIURETICS

MIS-DIAGNOSED ESSENTIAL HYPERTENSION

CYCLICAL PEDAL EDEMA

"WEIGHT LOSS" REGIMENS

CHRONIC CONGESTIVE HEART FAILURE

CIRRHOSIS OF LIVER

NEPHROTIC SYNDROME

PARENCHYMAL RENAL DISEASE

- POLYCYSTIC KIDNEY DISEASE
- GLOMERULONEPHRITIS
- PYELONEPHRITIS

Martinez-Maldonado M:
Tex Med 69:83, 1973

From Ref. 89

in this regard and may mask a salt depleted state because the continued urinary output is interpreted as reflecting adequate stores of body salt and water. This table illustrates some of the situations in which volume depletion may be induced through the ill advised use of diuretics. Of particular note is the circumstance where the effective arterial blood volume is depleted as one might see in chronic congestive heart failure, the nephrotic syndrome or cirrhosis of the liver, but where the extracellular fluid volume is expanded. Here the use of diuretics by further depleting the effect of arterial blood volume will lead to organ underperfusion, a potential for developing serious problems with cardiac perfusion, cerebral perfusion and renal perfusion. In some instances of parenchymal renal disease, particularly those associated with salt wastage as polycystic kidney disease or pyelonephritis, diuretics may further exaggerate a salt wasting state of the type we have previously eluded to. In glomerulonephritis an ineffective arterial volume may exist because of hypoalbuminemia from the nephrotic syndrome and renal function may be worsened by depletion of the effect of arterial volume and consequent renal underperfusion.

89. Martinez-Maldonado M: Electrolyte disturbances resulting from diuretic therapy. Tex Med 69:83, 1973

90. Fichman MP, Vorherr H, Kleeman CR et al: Diuretic-Induced Hyponatremia. Ann Intern Med 75:853, 1971

91. Mataverde AQ, Abbasi AA, Hossain Z et al: Hydrochlorothiazide-Induced Water Intoxication in Myxedema. JAMA 230:1014, 1974

92. Sullivan RC, Freemon FR and Caranasos GJ: Complications from Diuretic Therapy with Ethacrynic Acid and Furosemide. So Med J 64:869, 1971

93. DeRubertis FR, Michelis MF, Beck N et al Complications of Diuretic Therapy: Severe Alkalosis and Syndrome Resembling Inappropriate Secretion of Antidiuretic Hormone: Metab 19:709, 1970

Salt wastage may also be incurred through the persistent administration or endogenous development of osmotic loads. Studies of the diabetic patient with profound glycosuria aptly demonstrated that on a salt restricted diet the continued excretion of sodium and weight loss occurred.

94. Atchley DW, Loeb RF, Richards DW et al: On Diabetic Acidosis, A Detailed Study of Electrolyte Balances following the Withdrawal and Reestablishment of Insulin Therapy. J Clin Invest 12:297, 1933

Increased urea loads may promote continued sodium excretion as is eluded to in one of the mechanisms in the post obstructive diuresis. In addition, increased urea loads may occur as a consequence of excessive nitrogen intake as may be seen in some instances of the feeding of artificial diets to patients in an attempt to improve overall nutrition. The diets however administered in such excessive doses as to promote the ongoing excretion of sodium via the osmotic effect of urea production.

95. Rapoport S, Brodsky WA, West CD et al: Urinary Flow and Excretion of Solutes during Osmotic Diuresis in Hydropenic Man. Am J Physiol 156:433, 1949

96. Mudge GH, Foulks J and Gilman A: Effect of Urea Diuresis on Renal Excretion of Electrolytes. Am J Physiol 158:218, 1949

The continued loss of hydrochloric acid from the stomach through nasogastric suction or vomiting leads to the generation of large amounts of sodium bicarbonate in the parietal cells of the antrum of the stomach. This sodium bicarbonate then is picked up by the circulation and most is excreted into the urine. The amount of bicarbonate produced may exceed the renal reabsorptive capacity for bicarbonate in the proximal tubule and the bicarbonate then becomes an unabsorbable anion, and a potent osmotic agent. It then obligates the excretion of cation which is usually either sodium or potassium. This may result in the continued elaboration of a reasonable urine volume which might be interpreted as reflecting an adequate intravascular volume but in fact would be deceptive, being only perpetuated by the osmotic agents in the urine and further promote sodium loss. The table by Black illustrates the retention of sodium, potassium and chloride that occurred in five patients who presented with pyloric stenosis and shows the net retention of electrolytes during the five days post-operatively.

Cumulative Retention of Electrolytes
During Period of Observations
(mEq.)

Case number	*Na*	*K*	*Cl*
Patients with clinical pyloric stenosis:			
1	−14	+808	+746
2	+297	+218	+279
3	+1,762	+57	+1,890
4	+602	+255	+770
5	+213	+195	+376
Partial stenosis found at operation:			
6	+42	+1	+108
7	+110	+182	+117
Gastrectomy; stenosis absent:			
8	+82	+32	+137
9	+207	+68	+363
10	+122	+12	+124
11	+43	−71	+50

From Ref. 97

This is in contrast to patients who had gastrectomies where no stenosis was present who retained an average of 125 mEq of sodium, 13 mEq of potassium and 181 mEq of chloride with an attempt to manage the fluid and electrolytes in a similar manner during the post-operative period. This study suggests, but of course does not prove, that salt wastage was going on during the interval prior to surgery.

Sulfonamides may cause a substantial osmotic load under very unusual circumstances. This is generally in the patient with a large burn involving more than 40% of the total body surface area where large amounts of sulfonamides are applied to the burn would and absorbed through the wound systemically. One of the agents, mafenide acetate is particularly soluble, readily absorbed, and readily excreted by the kidneys. Up to 200 gm of this material may be applied topically per day, which represents a potential osmolar load of 1000 milliosmols. The study reported below describes the excretion of a millimole/min of this

substance after a single application of the mafenide acetate. In addition, the substance is a potential carbonic anhydrase inhibitor adding the additional load of bicarbonate as an osmotic agent in addition to the mafenide acetate.

The excessive administration of phosphate in parenteral hyperalimentation fluids may be a potential source of excessive osmotic loads. These salts administered as potassium phosphate salts may be either given orally or parenterally. Lithium salts major renal effect is the inhibition of the effect of antidiuretic hormone also may promote increased sodium excretion. A report by Fetner and White document the increased excretion of sodium after the administration of lithium in a patient with the inappropriate secretion of antidiuretic hormone with the induction of a state of salt depletion associated with postural hypotension. This natriuretic effect was spontaneously overcome and salt retention ensued and the study by Thomsen in rats also suggests lithium has a natriuretic effect.

97. Black DAK and Jepson RP: Electrolyte Depletion in Pyloric Stenosis. Quart J Med 23:367, 1954

98. White MG and Asch MJ: Acid-base Effects of Topical Mafenide Acetate in the Burned Patient. N Eng J Med 284:1281, 1971

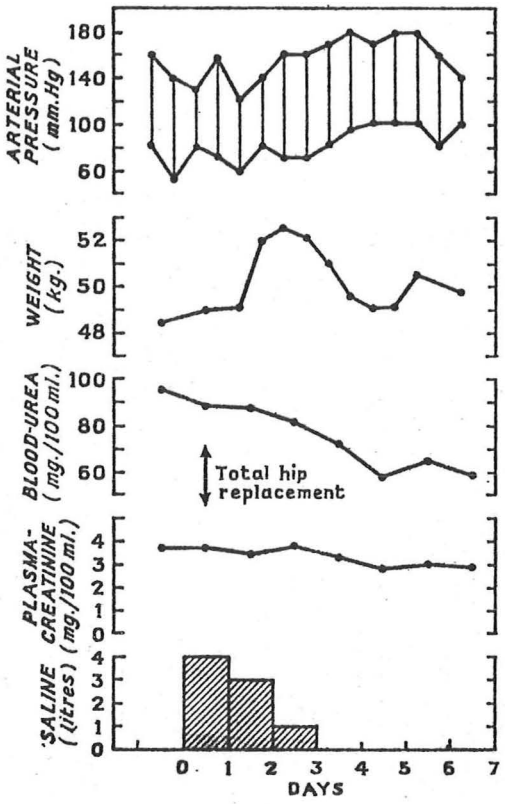
99. Fetner CD and White MG: Treatment of the Syndrome of Inappropriate Secretion of Antidiuretic Hormome with Lithium Carbonate. N Eng J Med 292:390, 1975.

100. Thomsen K, Jensen J and Olesen OV: Lithium-induced Loss of Body Sodium and the Development of Severe Intoxication in Rats. Acta Pharmacol et Toxicol 35:337, 1974

Management of Salt Wasting States

Substantiation of the diagnosis of salt wastage is essential before management can be instituted. The great hazard that one is confronted with is the differentiation of salt wastage from either a spontaneous diuresis or the inappropriate administration of salt. All three result in the excretion of large amounts of sodium chloride in the urine. It is mandatory to demonstrate that the continued elaboration of salt in excess of intake is associated with evidence of organ underperfusion. This is most easily assessed by the response of the blood pressure to the upright or semi-upright position and a longitudinal assessment of renal function. In general, management consists of providing an adequate salt intake to restore extracellular fluid volume deficits and to prevent subsequent depletion from occurring. In addition, if the possibility of mineralocorticoid deficiency is present, such a deficiency should be documented and then the mineralocorticoid administered.

A lack of awareness of a potential salt wasting state, particularly in patients with chronic kidney disease may result in the needless induction of complications. This particularly applies to the patient with renal insufficiency and a salt wasting defect who is subjected to surgery. These patients should not be volume contracted prior to the surgical procedure. Intravenous administration of sodium chloride salts while fasting and cleansing of the bowel have been induced is appropriate. The accompanying figure, perhaps an extreme example of the administration of fluids in the patient with chronic renal failure, demonstrates that by the adequate administration of fluids and an increase in weight, that renal function was maintained in a stable state and did not decrease.



Tasker PRW, MacGregor GA, and de Wardener HE: Prophylactic Use of Intravenous Saline in Patients with Chronic Renal Failure Undergoing Major Surgery. Lancet 911:2, 1974