SODIUM DEPLETION IN ADRENALECTOMIZED HUMANS [1]

By Mortimer B. Lipsett [2] and Olof H. Pearson

(From the Division of Clinical Investigation, Sloan-Kettering Institute for Cancer Research; and the Department of Medicine, James Ewing Hospital, New York, N. Y.)

(Submitted for publication September 19, 1957; accepted June 26, 1958)

Experimental sodium depletion has seldom been studied in man due to the considerable difficulties in inducing loss of sodium. The efficient renal conservation of sodium promoted by aldosterone precludes the development of sodium deficiency via urinary excretion. Salt loss has been achieved by prolonged sweating (1) but this is a relatively vigorous procedure involving complex compensations by the cardiovascular system, kidneys and adrenal glands. Renal salt loss can be easily obtained, however, in adrenalectomized patients receiving maintenance doses of cortisone. Such a subject is relatively normal with respect to a number of metabolic functions (2) but is unable to adjust completely to a low salt diet.

The purpose of this study was to analyze some of the phenomena of sodium depletion as they occur in the adrenalectomized patient maintained with cortisone alone. These were: *1*) the relationship of the initial total exchangeable sodium to the magnitude of the salt loss necessary to induce hyponatremia; *2*) the mechanism of the development of hyponatremia during sodium depletion; and *3*) the question of "inactivation" of intracellular cation.

METHODS

The studies were carried out on six adults on the Metabolic Unit of the James Ewing Hospital. Adrenalectomy had previously been performed on five of the patients for control of metastatic cancer. Two of these patients, T. P. and E. G., had subsequently been subjected to hypophysectomy during relapse. The sixth patient, L. V., had developed classical Addison's disease during the year preceding this study. All patients had normal renal function as measured by blood urea nitrogen (BUN), serum creatinine and 24-hour endogenous creatinine clearance. Only Patient T. P. had edema; this was limited to the arm and was presumably due to recurrent breast cancer involving the chest wall and axilla.

The patients were placed on a low salt diet (6 to 15 mEq. of sodium daily) supplemented with weighed amounts of sodium chloride during the periods of normal salt intake. Water intake was uncontrolled as the analyzed sodium content was insignificant. The studies were performed only during the cool months in order to minimize sweat losses of sodium. The patients were ambulatory but their activity was generally restricted. Each subject was fed from the same lot of food throughout the study and sample diets were analyzed every two weeks. The sodium and potassium content of rejected food was calculated on the basis of these analyses. The dosage of cortisone acetate was constant throughout except in L. V. and is recorded in Table I. No patient received any salt-retaining hormone.

Methods used in this laboratory for the determination of sodium, potassium, chloride, carbon dioxide content, creatinine and BUN have been described (3). Total exchangeable sodium was estimated by the method of Forbes and Perley (4). Urine osmolality was determined cryoscopically with the Fiske osmometer.

The initial body water was assumed to be 60 per cent of the body weight in R. D., a male, who was not sodium depleted. The initial body water in the three women was assumed to be 50 per cent of the body weight. This approximation is derived from an average body water in females of 55 per cent of the body weight and the consideration of sodium depletion prior to this study.

The changes in total base during the period of sodium depletion and at intervals during sodium repletion were calculated by the formula $bB = W_2[B_2] - W_1[B_1]$ (5), where W_1 and W_2 are the initial and final body waters, respectively, $[B_1]$ and $[B_2]$ the initial and final cation concentrations, respectively, and bB the predicted cation balance. The cation concentration is the sum of the serum sodium and potassium concentrations. The serum cation concentration on the first day of the repletion period of M. L. is an interpolated value, as the specimens for that day were lost.

RESULTS

The total exchangeable sodium (Na_e) was measured at the start of each period of sodium depletion. In Figure 1, these values are compared with the amount of salt lost during the experimental period of low sodium intake. For a more valid

[1] These studies were supported in part by grants from the National Cancer Institute of the National Institutes of Health (C-925), United States Public Health Service; the United States Atomic Energy Commission; the American Cancer Society, Inc.; and the Damon Runyon Memorial Fund.

[2] Present address: National Institutes of Health, Bethesda, Md.

TABLE I

Serum electrolytes and balance data in adrenalectomized patients during sodium depletion and sodium repletion

Patient	Cortisone acetate	Day	Wt.	Sodium			Potassium			Creatinine	Na	K	Cl	CO_2	Creatinine
				Intake	Urine	Feces	Intake	Urine	Feces						
	mg./day		*Kg.*	*mEq./24 hrs.*			*mEq./24 hrs.*			*mg./24 hr.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mg. %*
M. L.	50	1	65.5	12.1	103.7	1.62	32.0	62.0	8.5	799	135	6.2	105	27.2	1.2
		2	65.0	9.3	64.6	1.62	32.0	39.5	8.5	798					
		3	64.7	9.3	58.9	1.62	19.01	46.4	8.5	798	133	6.0	103		
		4	64.6	13.2	46.6	1.62	30.0	44.1	8.5	684					
		5	64.1	14.5	40.0	1.62	1.0	46.8	8.5	684	125				
		6	63.7	8.8	21.2	1.62	1.0	39.1	8.5	684	123	5.3	90		
		1	65.0	143.0	68.1	1.33	22.0	53.4	5.03	874					1.7
		2	65.2	138.0	75.2	1.33	37.0	39.1	5.03	874	112	5.6			
		3	64.4	146.0	134.0	1.33	40.0	48.5	5.03	874	121	5.5	94	23.7	1.4
		4	63.2	147.0	99.0	1.33	44.0	43.2	5.03	721					
		5	63.4	147.0	125.8	1.33	46.0	45.7	5.03	721					
		6	63.1	147.0	133.4	1.33	47.0	47.1	5.03	721					
		7	63.3	147.0	118.0	4.90	53.0	46.8	6.10	691	128	5.1	95	26.4	1.1
		8	62.8	148.0	100.0	4.90	53.0	42.4	6.10	691					
		9	63.2	148.0	116.3	4.90	53.0	54.4	6.10	691					
		10	63.6	250.0	175.4	5.60	53.0	59.5	5.60	710	132		102	25.5	1.0
		11	63.4	250.0	159.0	5.60	53.0	51.2	5.60	710					
		12	63.8	250.0	145.2	5.60	53.0	33.7	5.60	710					
		13	64.3	250.0	193.7	5.60	53.0	49.8	5.60	821	131	5.7	102		
		14	64.3	250.0	213.0	5.60	53.0	48.6	5.60	821					
		15	63.9	250.0	194.0	5.60	53.0	56.6	5.60	821					
			64.4								137	5.4	110	25.5	1.0
R. D.	75	1	52.7	12.7	145.0	0.70	103.0	58.5	8.50	887	139	5.6	110	24.0	1.1
		2	51.9	12.7	92.7	0.70	103.0	55.3	8.50	869					
		3	51.6	12.7	154.0	0.70	103.0	60.0	8.50	923	138	5.50			
		4	51.2	10.0	111.0	0.70	83.4	59.8	8.50	853					
		5	51.0	8.0	75.6	0.70	74.2	46.0	8.50	689					
		1		277.0	97.6	0.70	54.3	60.0	8.50	832	120	5.70	96		1.4
		2	51.2	138.0	110.0	0.50	102.0	87.0	7.4	832	122	6.60	91	23.0	
		3	51.3	140.0	125.0	0.50	103.0	88.0	7.4	762	127	5.62	104	25.0	1.2
		4	51.1	140.0	125.0	0.50	103.0	88.0	7.4	762					
		5	50.2	139.0	125.0	0.50	90.0	88.0	7.4	762	134	5.93			
		6	50.9	139.0	128.0	0.50	102.0	69.0	7.4	884					
		7	51.1	135.0	128.0	0.50	90.0	69.0	7.4	884					
			51.2								137	5.42	104		1.0
T. P.	75	1	65.6	14.5	74.9		93.1	54.2		680	138	4.75	100	30.7	1.0
		2	65.6	14.5	78.8		93.1	90.9		680					
		3	64.8	14.5	65.7		93.1	87.4		680					
		4	65.1	14.5	42.7		93.1	57.0		540	133	5.20			
		5	64.8	14.5	46.7		93.1	88.3		540					
		6	64.7	5.6	24.0		42.2	43.9		540					
		7	64.4	2.1	14.7		31.1	38.9		534	130	5.20	100	28.0	1.8
		1	63.6	110.0	46.8		54.0	65.4		584	125	5.95	96	31.0	1.4
		2	64.1	116.0	65.0		93.1	77.8		584					
		3	63.7	116.0	84.0		93.1	78.9		632					
		4	64.8	116.0	94.0		93.1	86.5		632	135	5.60			1.5
		5	64.2	116.0	94.5		93.1	89.1		632					
		6	63.5	116.0	75.7		93.1	86.3		632					
			63.8								138	5.99	103	25.0	1.2
E. G.	75	1	53.6	6.5	149.0		48.2	62.0		529	134	5.61			0.9
		2	53.1	6.5	88.0		48.2	49.4		491					
		3	52.8	6.5	57.0		48.2	44.1		355	130	5.48			1.3
		4	51.5	6.5	57.8		46.5	39.5		368					
		1	50.8	153.0	102.0		37.8	49.3		661	123	6.47			1.3
		2	51.7	119.0	75.1		47.0	51.6		665	130	7.31			
		3	51.0	119.0	65.1		37.0	35.3		421	127	6.33			1.0
		4	51.2	119.0	54.1		47.0	40.8		356					
		5	51.7	119.0	53.3		47.0	45.8		378	130	6.70			1.2
		6	51.9	119.0	80.6		47.0	45.6		389					
		7	51.6	119.0	76.5		47.0	49.1		419					
		8	51.8	119.0	62.8		47.0	40.4		426					
			51.9								136	6.10			1.0

TABLE I—*Continued*

Patient	Cortisone acetate	Day	Wt.	Sodium			Potassium			Creatinine	Na	K	Cl	CO_2	Creatinine
				Intake	Urine	Feces	Intake	Urine	Feces						
	mg./day		*Kg.*	*mEq./24 hrs.*			*mEq./24 hrs.*			*mg./24 hr.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mg.%*
L. V.	12.5	1–3	67.5	7.7	101.0	2.1	37.0	29.1	3.6	743	143	4.30	111	24.9	1.0
		4–6	65.5	7.7	52.1	2.1	37.0	34.8	3.6	764	140				
		7–9	64.8	7.7	28.7	2.1	37.0	36.8	3.6	636	137	5.45			
		10–12	63.8	7.7	36.6	2.1	37.0	34.1	3.6	670					1.1
		13–14	63.8	7.7	26.5	2.1	37.0	36.1	3.6	714	137	5.71			
		1–3	63.7	144.0	56.9	3.7	37.0	43.4	6.0	684	134	5.80	109	26.3	1.2
		4–6	53.6	144.0	95.7	3.7	37.0	45.9	6.0	678					
	50	7–9	63.2	144.0	113.0	2.1	37.0	45.6	2.9	780	139	5.32			
		10–12	63.7	144.0	137.0	2.1	37.0	40.6	2.9	874					
M. C.	75	1–3	51.2	9.6	46.3	1.5	58.0	46.2	16.7		141	5.90	106	28.6	1.1
		4–6	50.6	9.6	27.8	1.5	58.0	53.1	16.7	853	139	5.02	105	28.1	1.2
		7–9	50.3	9.6	32.1	1.5	58.0	46.5	15.0	678					
		10–12	49.7	13.0	39.3	1.5	73.0	62.9	15.0	578					
		13–15	49.5	13.0	43.4	2.9	73.0	55.3	14.8	685					
		16–18	49.9	13.0	23.9	2.9	73.0	44.0	14.8	613					
		19–21	48.9	13.0	22.4	2.1	73.0	50.2	12.5	680					
		22–24	48.3	13.0	26.8	2.1	73.0	55.4	12.5	605	136	6.45	102	23.7	1.5
		25–27	48.3	13.0	24.0	2.0	73.0	49.3	18.9	514					
		28–31	48.7	13.0	16.6	2.0	73.0	43.6	18.9	517					
		1–3	47.5	115.0	35.0	1.4	73.0	33.7	12.0	479					
		4–6	48.4	84.2	40.8	1.4	61.1	31.9	12.0	475	132	5.60	96	19.5	1.7
		7–9	47.8	113.0	35.3	1.4	61.7	34.0	12.0	481					
		10–12	48.2	112.0	30.0	3.2	59.8	33.7	21.6	519					
		13–15	48.5	113.0	22.0	3.2	65.3	20.1	21.6	577					
			49.5								146	5.59	106	21.6	1.2

comparison among the patients, these figures have been expressed as a percentage of the predicted normal Na_e using an arbitrary Na_e of 40 mEq. per kilogram of body weight. Thus the light vertically-striped areas in Figure 1 indicate the degree of sodium depletion experienced by these patients before the onset of the period of low salt intake. The dotted cross-hatched area expresses the amount of sodium lost during the balance study as a percentage of the predicted Na_e for each patient.

Patients M. L., T. P. and E. G., who had advancing metastatic cancer, entered the hospital severely depleted of sodium. In spite of these greatly decreased intitial Na_e's, the serum sodium concentrations were within the normal range (Table I). After the loss of relatively little additional sodium (268 mEq., 282 mEq. and 333 mEq., respectively), severe hyponatremia developed (Table II). At this time, six, seven and four days, respectively, the patients had become anoretic, weak and lethargic, and two patients demonstrated muscular cramps and postural hypotension.

In contrast to these subjects, Patients L. V. and M. C. developed symptoms of salt depletion slowly, and in neither case were the symptoms severe nor the hyponatremia profound, although 630 and 614 mEq. of sodium, respectively, were lost (Table II). Their periods of salt depletion were terminated because we did not feel justified in further extending the length of disability. It seemed evident to us, however, that further salt restriction would have been necessary to reach the clinical states experienced by the previous three patients. The initial Na_e was higher in these two latter patients, being normal in M. C. Both patients reduced their urinary losses of sodium gradually but not sufficiently to achieve sodium balance.

The sixth patient, R. D., had a normal Na_e initially, but very rapidly developed severe hyponatremia with the full clinical syndrome. This patient exhibited only minimal renal conservation of sodium and 557 mEq. of sodium was lost in five days (Tables I and II).

As one of the patients, T. P., also had moderately severe diabetes insipidus, it was possible to assess partially the role of antidiuretic hormone in the water retention noted during the development of hyponatremia. In Figure 2 the urine osmolality, urine volume and the 24 hour millios-

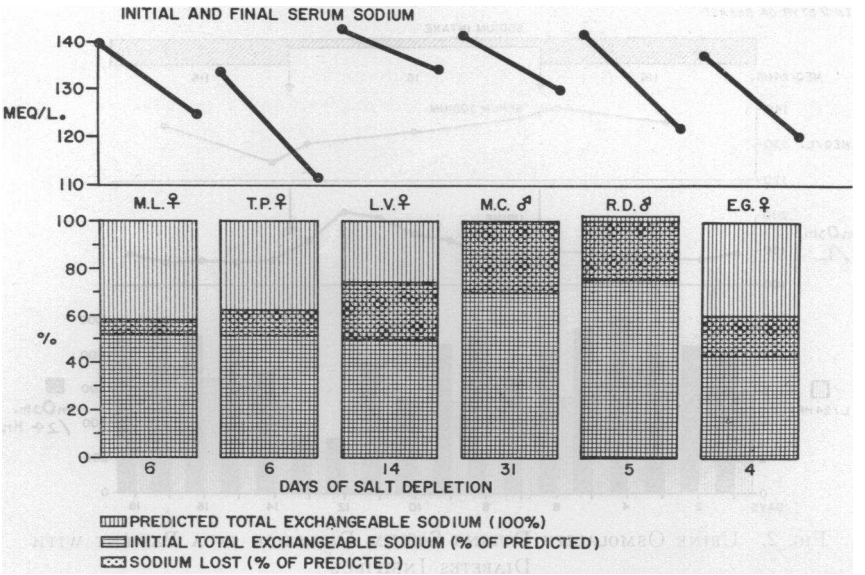

FIG. 1. RELATIONSHIP OF INITIAL Na_e TO SODIUM LOSS AND HYPONATREMIA

mol excretion are plotted throughout the study. The urine volume decreased markedly as a result primarily of poor food intake and correspondingly fewer solutes presented for excretion. Urine osmolality increased slightly, but only to a maximum of 205 milliosmols per liter, a concentration considerably hypotonic to plasma. Therefore, in this patient at least, water retention relative to sodium excretion was noted in the absence of a hypertonic urine and probably at only minimal levels of antidiuretic hormone.

In all patients the glomerular filtration rate (GFR), as estimated by 24 hour endogenous creatinine clearance, fell *pari passu* with sodium depletion and contraction of plasma volume (Table III). This makes interpretation of small changes in urine osmolality of questionable significance, as a rise in urine osmolality may result from a markedly decreased GFR (6).

ΔB_i, the algebraic difference between the predicted cation balance and the observed cation balance, $b_{(Na+K)}$, is recorded in Table III for four

TABLE II

Summary of balances of Na and K in adrenalectomized patients on a low sodium diet and after sodium repletion

Patient	Sodium intake	Days	Initial Na_e	ΔNa	ΔK	Endogenous creatinine clearance at end of period (% initial value)
		no.	*mEq.*	*mEq.*	*mEq.*	
M. L.	Low	6	1,570	− 268	−214	56
	suppl.	15		+ 704	− 89	111
T. P.	Low	7	1,640	− 282	+ 22	42
	suppl.	6		+ 218	− 13	71
E. G	Low	4	1,280	− 333	− 36	48
	suppl.	8		+ 401	− 65	73
R. D.	Low	5	2,270	− 557	+136	55
	suppl.	7		+ 265	+ 42	98
L. V.	Low	14	2,080	− 630	−117	75
	suppl.	12		+ 486	− 9	100
M. C.	Low	31	2,070	− 614	+ 81	40
	suppl.	15		+1,091	+267	69

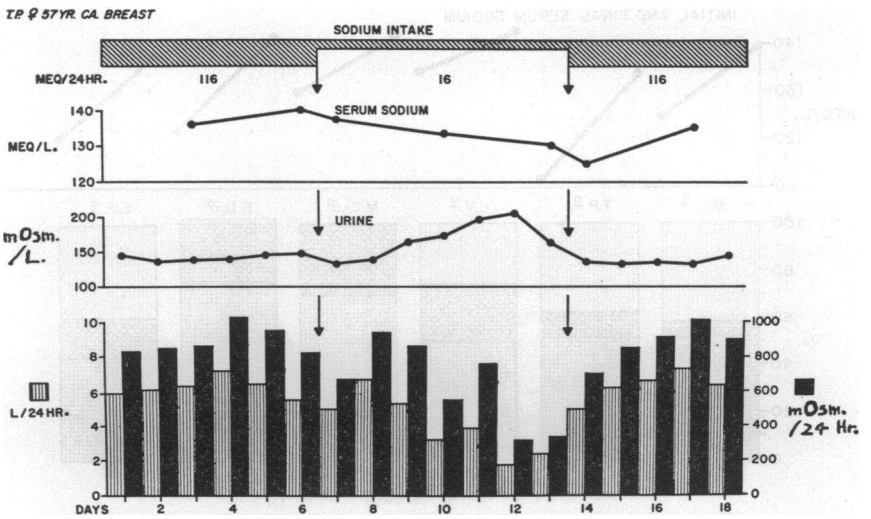

FIG. 2. URINE OSMOLALITY DURING SODIUM DEPLETION IN A PATIENT WITH DIABETES INSIPIDUS

patients. The periods of study were too long in the other two patients for the assumption regarding the equivalence of weight change and alteration in body water to be applicable (*vide infra*). Calculations were made at various intervals during periods of sodium depletion and repletion as well as for the entire period. The predicted cation balance during salt depletion in each case was considerably greater than that measured. This phenomenon occurred in large part during the last interval of the depletion period.

During salt repletion, the converse obtained: Less cation was retained than that predicted. The largest discrepancy in three of the four patients was observed during the first interval, *i.e.*, immediately after increasing the sodium intake.

Similarly, a comparison of the observed serum cation concentration with that calculated for the

TABLE III

Observed vs. predicted cation balances during depletion and repletion of sodium

	Depletion						Repletion					
Patient	Days	Serum cation conc.	Predicted* serum cation conc.	bB	$b_{(Na+K)}$	ΔB_i	Days	Serum cation conc.	Predicted* serum cation conc.	bB	$b_{(Na+K)}$	ΔB_i
		mEq./L.	*mEq./L.*	*mEq.*	*mEq.*	*mEq.*		*mEq./L.*	*mEq./L.*	*mEq.*	*mEq.*	*mEq.*
T. P.	1–3	138	140	−230	−160	− 70	1–3	141	131	+470	+134	+336
	4–7	131	142	−420	−102	−318	4–6	144	148	− 50	+ 71	−121
	1–7	131	144	−650	−262	−388	1–6	144	137	+420	+205	+215
E. G.	1–2	135	135	−170	−259	+ 89	1–4	137	131	+320	+166	+154
	3–4	129	145	−500	−110	−390	5–8	142	143	+ 50	+170	−120
	1–4	129	141	−670	−369	−301	1–8	142	146	+370	+336	+ 34
R. D.	1–2	144	147	−190	−139	− 51	1–4	140	134	+420	+243	+177
	3–5	126	137	−610	−282	−328	5–7	142	142	+ 70	+ 64	+ 6
	1–5	126	139	−800	−421	−379	1–7	142	136	+490	+307	+183
M. L.	1–2	139	138	−180	−206	+ 26	1–6	133	134	+130	+153	− 23
	3–6	122	128	−510	−276	−234	7–9	138	135	+160	+ 91	+ 69
	1–6	122	128	−690	−482	−208	10–15	137	145	+270	+371	−101
							1–15	143	143	+560	+615	− 55

* $[B_2] = \frac{W_1[B_1] + b_{(Na+K)}}{W_2}$.

end of the depletion period showed a marked discrepancy in each case. During the periods of repletion, this calculation was made at various time intervals and the discrepancies were likewise marked.

DISCUSSION

To our knowledge no previous study has related the total exchangeable sodium and the amount of sodium lost to the development of hyponatremia. It seems evident that in the presence of a depleted total body sodium, small additional losses can rapidly lead to severe hyponatremia. When this occurs about 50 per cent of the total exchangeable sodium has been lost. This situation is the prototype of the spontaneous development of the hyponatremic crisis of Addison's disease. The patient with Addison's disease may endure a gradual depletion of body sodium meanwhile maintaining a normal serum sodium by gradual contraction of plasma volume and extracellular fluid. The imposition of a period of low salt intake or additional salt loss, such as occurs with a gastrointestinal upset, would then quickly precipitate severe hyponatremia.

In addition to the amount of sodium depletion necessary to produce hyponatremia, the rate of salt loss may also influence the degree of hyponatremia and the severity of clinical manifestations. Thus, Patients M. C. and L. V. sustained large losses of sodium, 614 mEq. and 630 mEq., respectively, which occurred gradually and resulted in only modest depressions of the serum sodium concentration. The slow loss of sodium which must have occurred in Patients T. P., M. L. and E. G. prior to the study had not led to hyponatremia.

On the other hand Patient R. D., who had an initial normal Na_e, lost 557 mEq. in five days and the serum sodium level dropped from 139 to 120 mEq. per liter. Nadal, Pedersen and Maddock (7) depleted two normal men of sodium by jejunal drainage causing sodium losses of 365 and 391 mEq. These losses occurred in four and five days, respectively, and although the magnitude of the salt loss was not great, the serum sodium concentrations reached 119 and 117 mEq. per liter. McCance's (1) two studies are intermediate in time so that losses of 980 mEq. and 765 mEq. of sodium in periods of 11 days led to decreases in the serum sodium of 14 mEq. and 13 mEq. per liter.

As McCance has pointed out (1), the loss of salt is accompanied by a loss of water so that the fluid lost during the initial stages of salt depletion is essentially extracellular fluid. With further sodium depletion, volume requirements are somehow "sensed" and water is retained relative to salt, resulting in hyponatremia. It has been suggested that antidiuretic hormone is secreted in response to these volume changes, thus facilitating the relative water retention (8) . The study with the patient with diabetes insipidus is pertinent to this problem. When she developed hyponatremia in response to sodium restriction, urine osmolality reached a value of only 205 milliosmols per liter. Although the hypophysectomized patient does not have a maximum diabetes insipidus (9), there was no evidence of release of antidiuretic hormone. The small increase in urine osmolality could easily have been due to the 60 per cent decrease in GFR (6).

Although any effect of antidiuretic hormone was minimal, a drop in serum sodium occurred. This implies the continued voluntary ingestion of water in the face of a falling serum sodium and presumably decreasing intracellular tonicity as well. Since thirst has generally been related to intracellular hypertonicity, this is a somewhat anomalous response. A sensation akin to thirst has previously been described after salt depletion in man (1) and suggested in the dog (10).

If an increased secretion of antidiuretic hormone was not responsible for the retention of water and development of serum hypotonicity, another mechanism must be sought. The potassium balance was positive during the period of sodium repletion, so that intracellular potassium loss cannot be invoked to explain the hyponatremia as has been suggested by Wynn and Houghton (11). Since the serum CO_2 content did not change, acidosis was probably not a factor. The marked decrease in GFR may be responsible for the water retention in view of studies relating impaired water diuresis to decreases of the GFR in man (12) and the sodium-depleted dog (13).

When salt was returned to these patients the immediate clinical results were dramatic. During the first day, often after retention of less than 70 mEq. of salt, the patients spontaneously vol-

unteered that the cramps had disappeared, dizziness was gone and appetite had returned. McCance (1) also observed similar dramatic effects after restoration of but a small part of the lost salt. These observations suggest that at some critical level of sodium depletion or hyponatremia symptoms become apparent.

The fall in GFR was most marked in those patients who became severely hyponatremic. The GFR in all patients, excluding L. V., averaged 46 per cent of the initial value at the end of the period of salt depletion. This, of course, is not a new finding and, indeed, an elevation of BUN or serum nonprotein nitrogen (NPN) has been seen in all studies of salt depletion. It is worth emphasizing that this finding should be important in the differential diagnosis of the hyponatremias. Thus, a normal serum BUN or NPN in the presence of severe hyponatremia effectively rules out sodium depletion as the cause of the hyponatremia. The converse is not necessarily true, *i.e.*, a patient with poor kidney function may develop dilution hyponatremia. This difference was noted by Wynn (14) in a discussion of hyponatremia. The reports of patients with "asymptomatic" hyponatremia (15, 16) are in accord with this suggestion.

The values obtained for ΔB_i require a discussion of the possible errors involved in these calculations. Assuming values other than 60 per cent for the initial body water will have little effect on bB, the predicted cation balance ($W_2[B_2] - W_1[B_1]$), and therefore little effect on ΔB_i. The most vulnerable assumption is that changes in body weight can be equated with changes in body water. We think this hypothesis is valid because of: *1*) the short periods of study, *2*) a previous control period of six days in three patients during which the weight remained stable, and *3*) the same caloric intake throughout the experiment with the exception of two or three days in three patients. The drop in caloric intake during this brief period of time is reflected in the decreased potassium intake (Table I). In two of the three patients, the drop in caloric intake was small. Patient M. L. had a decrease in caloric intake of 460 and 520 calories on Days Five and Six of the salt-depletion period. The possible weight loss due to this caloric deficit would only be of the order of 0.34 Kg. per day even if half of the calories were supplied by protein. Thus, in the patient with the largest possible weight loss due to poor food intake, the correction would not greatly alter the value for ΔB_i.

During the two days of decreased caloric intake, M. L. had a negative nitrogen balance of 4.2 and 3.1 grams of nitrogen, respectively. This would result in the loss of 21 mEq. of potassium. As this patient had the largest decrease in caloric intake, the possible potassium losses in the other patients due to catabolism of muscle nitrogen were small.

The other possible systematic error was unmeasured losses of sweat sodium. The limited activity and absence of visible sweat make it doubtful that more than 5 mEq. of sodium daily was lost by this route. However, even assuming four times this amount daily does not greatly alter the findings. Furthermore, unmeasured sweat sodium loss would increase ΔB_i during the repletion period. The fact that the large values for ΔB_i occurred during the two to three day interval at the end of the depletion period and at the start of the repletion period, makes the possible sweat losses of lesser significance.

Other errors, such as spontaneous fluctuations of weight and serum sodium, and analytical errors in the determination of sodium and potassium, are random. The uniformly negative values for ΔB_i during depletion and positive values during repletion make it improbable that random errors could account for these effects.

Yannet and Darrow (17) had observed that following acute sodium depletion in cats, the change in the concentration of base in tissue water was two-thirds as great as that predicted on the basis of intra- and extracellular isotonicity. Mellors, Muntwyler and Mautz (18) likewise noted that, on the average, the gain in intracellular water after sodium depletion in dogs was only 60 to 70 per cent of that predicted. Elkinton, Winkler and Danowski (5) found significant discrepancies between the observed and predicted cation balances in a variety of experiments with dogs and humans. In two dogs subjected to sodium depletion, ΔB_i was negative following depletion and positive after repletion. Schwartz, Bennett, Curelop and Bartter (19) similarly observed a large discrepancy between sodium loss and calculated intracellular tonicity. Thus, the findings of our study have ample precedent.

The values calculated for ΔB_i should be of the same magnitude for the periods of depletion and

repletion if the cells had returned to their original state by the end of the study. This was not so in these experiments and the reasons for this are not clear. It is an inadequate explanation to suggest that insufficient time was allowed during the repletion period as the maximum values for ΔB_i were noted during the first interval of this period.

The physical meaning of negative values for ΔB_i has not been clearly defined. It was proposed (5) that this represented the amount of cation rendered osmotically inactive. If an original isoosmotic state and rapid attainment of intra- and extracellular isotonicity is accepted, then this conclusion is warranted. Alternative hypotheses are that during severe salt depletion the cell is able to maintain an internal environment hypertonic to the interstitial fluid or that an initially hypertonic intracellular milieu was increased with salt loss. Our data do not permit us to distinguish among these theories. In any case, it is of interest that this phenomenon may be viewed as a homeostatic mechanism in that maintenance of extracellular fluid volume is permitted at a lower cation concentration with less water entering the intracellular compartment.

Leaf, Chatillon, Wrong and Tuttle (20) and Wynn (21) have shown that large water loads are distributed throughout the total body water and that the predicted cation concentrations closely agree with the observed cation concentrations. In the postoperative period as well, this agreement is good (11). From these data Wynn and Houghton (11) concluded that neither inactivation of cell cation nor departure from intracellular isotonicity occurs. In view of the consistent findings during sodium depletion, these possibilities must still be seriously considered.

SUMMARY AND CONCLUSIONS

Negative sodium balances varying from 241 mEq. to 630 mEq. have been produced in adrenalectomized patients by a low salt diet. As these patients were receiving constant doses of cortisone, the changes noted could be ascribed solely to the effects of sodium depletion. The induction of significant hyponatremia depended upon the extent of depletion of body sodium and possibly on the rate of depletion as well.

The development of hyponatremia was shown to occur in the absence of antidiuretic hormone. The relative water retention which must occur as hyponatremia develops was related to the marked decrease in glomerular filtration rate.

When the observed cation balances were compared with those predicted from the changes in body water and serum cation concentrations, marked discrepancies were noted. These data support the suggestion that under appropriate circumstances either inactivation of intracellular cation or differences between intra- and extracellular tonicity can be demonstrated.

ACKNOWLEDGMENT

The authors wish to acknowledge the assistance of Miss Marie Restuccia, Mrs. Lois Stroub and Miss Constance Swedlin in various phases of these studies.

REFERENCES

1. McCance, R. A. Experimental sodium chloride deficiency in man. Proc. roy. Soc. B 1936, 119, 245.
2. Hollander, V. P., West, C. D., Whitmore, W. F., Jr., Randall, H. T., and Pearson, O. H. Physiological effects of bilateral adrenalectomy in man. Cancer 1952, 5, 1019.
3. Eliel, L. P., and Pearson, O. H. The metabolic effects of adrenocorticotropic hormone (ACTH) in a patient with Cushing's syndrome and acromegaly. J. clin. Endocr. 1951, 11, 913.
4. Forbes, G. B., and Perley, A. Estimation of total body sodium by isotopic dilution. I. Studies on young adults. J. clin. Invest. 1951, 30, 558.
5. Elkinton, J. R., Winkler, A. W., and Danowski, T. S. Inactive cell base and the measurement of changes in cell water. Yale J. Biol. Med. 1944, 17, 383.
6. Berliner, R. W., and Davidson, D. G. Production of hypertonic urine in the absence of pituitary antidiuretic hormone. J. clin. Invest. 1957, 36, 1416.
7. Nadal, J. W., Pedersen, S., and Maddock, W. G. A comparison between dehydration from salt loss and from water deprivation. J. clin. Invest. 1941, 20, 691.
8. Leaf, A., and Mamby, A. R. An antidiuretic mechanism not regulated by extracellular fluid tonicity. J. clin. Invest. 1952, 31, 60.
9. Lipsett, M. B., and Pearson, O. H. Further studies of diabetes insipidus following hypophysectomy in man. J. Lab. clin. Med. 1957, 49, 190.
10. Cizek, L. J., Semple, R. E., Huang, K. C., and Gregersen, M. I. Effect of extracellular electrolyte depletion on water intake in dogs. Amer. J. Physiol. 1951, 164, 415.
11. Wynn, V., and Houghton, B. J. Observations in man upon the osmotic behaviour of the body cells after trauma. Quart. J. Med. 1957, 26, 375.

12. Kleeman, C. R., Epstein, F. H., and White, C. The effect of variations in solute excretion and glomerular filtration on water diuresis. J. clin. Invest. 1956, **35**, 749.
13. Cizek, L. J., and Huang, K. C. Water diuresis in the salt-depleted dog. Amer. J. Physiol. 1951, **167**, 473.
14. Wynn, V. Water intoxication and serum hypotonicity. Metabolism 1956, **5**, 490.
15. Sims, E. A. H., Welt, L. G., Orloff, J., and Needham, J. W. Asymptomatic hyponatremia in pulmonary tuberculosis. J. clin. Invest. 1950, **29**, 1545.
16. Harrison, H. E., Finberg, L., and Fleishman, E. Disturbances of ionic equilibrium of intracellular and extracellular electrolytes in patients with tuberculosis meningitis. J. clin. Invest. 1952, **31**, 300.
17. Yannet, H., and Darrow, D. C. The effect of depletion of extracellular electrolytes on the chemical composition of skeletal muscle, liver and cardiac muscle. J. biol. Chem. 1940, **134**, 721.
18. Mellors, R. C., Muntwyler, E., and Mautz, F. R. Electrolyte and water exchange between skeletal muscle and plasma in the dog following acute and prolonged extracellular electrolyte loss. J. biol. Chem. 1942, **144**, 773.
19. Schwartz, W. B., Bennett, W., Curelop, S., and Bartter, F. C. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Amer. J. Med. 1957, **23**, 529.
20. Leaf, A., Chatillon, J. Y., Wrong, O., and Tuttle, E. P., Jr. The mechanism of the osmotic adjustment of body cells as determined *in vivo* by the volume of distribution of a large water load. J. clin. Invest. 1954, **33**, 1261.
21. Wynn, V. A metabolic study of acute water intoxication in man and dogs. Clin. Sci. 1955, **14**, 669.