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A Syndrome of Renal Sodium Loss and Hyponatremia Probably Resulting from Inappropriate Secretion of Antidiuretic Hormone*

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This paper is a report of studies of two patients with bronchogenic carcinoma in whom hyponatremia developed as the result of unexplained failure of renal sodium conservation. The data indicate that sustained inappropriate secretion of antidiuretic hormone was probably responsible for the disorder of sodium metabolism. The physiologic abnormality appears to be analogous to that which can be produced by the continuous administration of pitressin® and water to normal subjects.

CASE REPORTS

CASE I. W.A., a sixty-year old hat cleaner, complained of coughing up bright red blood for the previous six weeks, and loss of 15 pounds of weight. On physical examination, he was well nourished. The blood pressure was 120/70 mm. Hg. There was marked clubbing of the fingers and toes which the patient said had been present all his life. Physical and neurologic examination was otherwise within normal limits.

Initial routine laboratory studies revealed no abnormalities in the hemogram. Urine examination was negative. Intravenous pyelogram revealed normal structure and excellent dye concentration in both kidneys.

X-ray revealed a 4 by 5 cm. ill-defined mass in the region of the right pulmonary artery. A biopsy by bronchoscope demonstrated anaplastic carcinoma of the right main stem bronchus, and an exploratory thoracotomy revealed an inoperable tumor at the right hilum infiltrating the esophagus and aorta. In the postoperative period empyema developed, which was satisfactorily controlled with antibiotics and saline solution irrigations. Two weeks after operation serum electrolytes and protein concentrations were measured as a routine procedure. The following values were obtained: sodium, 121 mEq./L.; potassium, 4.6 mEq./L.; chloride, 88 mEq./L.; carbon dioxide content, 24 mEq./L., calcium, 10.0 mg. per cent; inorganic phosphate, 4.0 mg. per cent; albumin, 2.1 gm. per cent; globulin, 3.7 gm. per cent. The hemoglobin was 9.8 gm. per cent. The patient was given small amounts of normal saline solution and on the following day his serum sodium was 114 mEq./L. and his blood

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AUTHOR COMMENTARY

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In 1955, a patient with bronchogenic carcinoma was admitted to the New England Medical Center with a puzzling syndrome of severe, unexplained hyponatremia and renal salt wasting. His BP was normal, and there was no evidence of volume depletion. Detailed studies revealed normal renal and adrenal function. The blood urea nitrogen concentration was notably low at 6 to 8 mg/dl. No explanation was at hand to account for the salt-wasting disorder, but the findings were similar to those in several puzzling cases reported in association with meningitis, pulmonary tuberculosis, and bronchogenic carcinoma.

Absent any hypothesis to account for this mysterious disorder, we decided simply to place the patient on a balance study using a constant diet (but not a constant water intake). Our hope was that by careful observation, the underlying forces promoting sodium excretion would reveal themselves, perhaps in response to maneuvers such as salt loading and DOCA administration. Such proved not to be the case. After 36 days of meticulous observation, we were still at sea. The serum sodium fluctuated between 136 and 103 mEq/L without an apparent explanation. Sodium infusions raised the serum sodium concentration transiently, but the sodium load was promptly excreted. At the end of the studies, we still had no answer, but in reviewing the data for the entire month, one fact suddenly took hold in my mind. Despite the dramatic reduction in the serum sodium concentration, the urine osmolality remained consistently hypertonic to the plasma, thus providing compelling evidence for the presence of antidiuretic hormone (ADH). Taken together with the evidence of normal volume status and BP as well as normal kidney and adrenal function, it seemed almost certain that the syndrome was accounted for by inappropriate

urea nitrogen was 9 mg. per cent. The urine sodium concentration was 70 mEq./L. At this time the physical examination was within normal limits. The blood pressure was 124/68 mm. Hg. Skin turgor and hydration were good. There was no abnormal pigmentation and axillary and pubic hair were normal. During the next two days he was given hypertonic sodium chloride, despite which his serum sodium concentration fell to 103 mEq./L. During this time the patient was asymptomatic. He was then given small doses of DOCA® and very large amounts of supplementary salt. Three days later metabolic studies were begun as described under "Results." On the first day of these studies 20 mg. Of DOCA were administered.

The patient was discharged from the hospital two months later. It was found that on salt intake *ad libitum* and slightly restricted fluid intake his serum sodium concentration could be maintained at normal or near normal values without steroids. During the next three months he was readmitted on two occasions for further observation. His final admission occurred eight months after the initial studies and three months after his last period of observation. He was emaciated, and had severe diarrhea and jaundice. Despite supportive therapy his condition progressively deteriorated, and he died three weeks after admission.

Autopsy revealed extensive bronchogenic carcinoma involving numerous mediastinal lymph nodes and the pericardium and invading and obscuring the vagus nerves. Metastases had obstructed the common bile duct and the pancreatic duct. There was extensive invasion of the adrenal area by metastatic tumor: the 5 to 10 per cent of the one adrenal cortex which was found was histologically normal. There were scattered metastases in the kidneys, which were otherwise grossly and microscopically normal. The brain showed metastases in the cerebral hemispheres and cerebellum, and bilateral cystic degeneration in the region of the basal ganglia. The pituitary gland was normal on gross and microscopic examination.

Case II. W. F., a fifty-six year old prizefighter, complained of anorexia, weakness and fatigability of one year's duration. Five months before admission the symptoms rapidly became more severe, and he was admitted to an outside hospital where he was observed to have severe hyponatremia (serum sodium 105 to 116 mEq./L.). The hyponatremia persisted despite administration of large quantities of salt and was accompanied by continuous loss of sodium in the urine. There was no clinical evidence of salt depletion. The non-protein nitrogen was 26 mg. per cent, and urinalysis was negative. He was found to have a duodenal ulcer. No adequate explanation could be found for the electrolyte disturbance, and he was admitted for further studies.

On physical examination, he was found to have normal skin turgor, normal body hair and no abnormal pigmentation. The blood pressure was 200/110 mm. Hg. Physical and neurologic examination was otherwise within normal limits. The urine was normal on numerous occasions; the hemogram was normal.

Chemical analyses revealed the following serum values: urea nitrogen, 12 mg. per cent; sodium, 133 mEq./L.; carbon dioxide content, 31 mEq./L.; potassium, 5.6 mEq./L.; glucose tolerance test, fasting 92 mg. per cent, thirty minutes 181 mg. per cent; sixty minutes 158 mg. per cent, 120 minutes 65 mg. per cent. Radioactive iodine uptake was normal (44 per cent) as was the basal metabolic rate (minus 5 per cent). Alterations in serum sodium concentration and results of studies of renal and adrenal function are described under "Results."

X-ray film revealed a prominence in the left hilum, thought to be pulmonary artery, and a duodenal ulcer. The sella turcica was normal.

secretion of antidiuretic hormone (SIADH)—i.e., secretion occurring even in the face of a sharply reduced serum osmolality and in the absence of hypovolemia. It seemed that the syndrome was a naturally occurring counterpart of an earlier physiologic study in which just such a picture was produced by administration of pitressin and water to normal subjects.

To say that I was excited by the prospect of carrying out the critical experiment of restricting fluid intake understates my feelings. I confess that by this time, I felt almost certain what the result would be. The patient was readmitted and placed on a 2000-cc fluid intake that was approximately twice what he had been ingesting. Characteristic sodium wasting was then observed along with a fall in serum sodium from 127 to 114 mEq/L.

Fluid was then sharply restricted ,and a sodium load was administered intravenously. In contrast to his previous response to such loads, sodium excretion fell to low levels and over the next 5 days the serum sodium concentration rose from 114 to 135 mEq/L. During this time, there was a weight loss of 5 kg. When the patient was again placed on a 2000-cc fluid intake, the urine sodium concentration rose dramatically and a large fraction of an administered sodium load was promptly excreted. A weight gain of 3 kg occurred, but there was no edema. On reflection, it became clear that SIADH does not require hypersecretion of ADH, only the presence of some ADH when none should be present. Thus, I realized that the diagnosis can be made in the face of a hypotonic urine as long as the urine is less than maximally dilute. In the absence of ADH assays, which were not available in 1956, I understood that I was not entitled to reach an unequivocal conclusion about the mechanism. The word "probably" was included in the title of the paper, although I admit that I had virtually no doubt in my mind about the nature of the disorder.

I confess that the apparent clarification of the mechanism of the salt wasting was one of the most exciting moments in my research career.

When I next saw Dr. Frederic Bartter of the National Institutes of Health, I told him about this case and discovered that he had studied a similar patient and had reached the same conclusion. We decided that we should report our studies jointly. We concluded that the previously unexplained cases of salt wasting in pulmonary tuberculosis and meningitis were also due to the inappropriate secretion of ADH.

Metabolic studies were instituted. Shortly thereafter periods of aphasia and disorientation began to appear with increasing frequency and duration. On the fifty-eighth hospital day biparietal burr holes were made revealing normal cerebrospinal fluid pressures. During the next two weeks clouding of the sensorium became progressively deeper and more continuous, and on the seventy-first hospital day a right facial paralysis and a right hemiparesis developed. Shortly thereafter the patient lapsed into coma. On his ninety-seventh hospital day he had hypotension for the first time, and two days later he began passing large amounts of dark red blood by rectum. This persisted, and despite numerous transfusions he failed rapidly; he died on his 101st hospital day.

Autopsy revealed a bronchogenic carcinoma measuring 8 by 4 cm. extending from the arch of the aorta to the left main stem bronchus, surrounding and compressing the left pulmonary artery and vein, involving numerous hilar lymph nodes, and invading and obscuring the vagus nerves. The sole extrathoracic metastasis was a single nodule, 0.8 cm. in diameter, in the medulla of the left adrenal gland, which was otherwise normal in size and structure, as was the right adrenal. The adrenal glands together weighed 15.5 gm. There were three duodenal ulcers one of which had eroded a small artery. The kidneys were grossly normal and showed only minimal arteriosclerosis. The brain showed encephalomalacia of the left internal capsule and caudate nucleus and of the right globus pallidus, pons and hippocampus. The pituitary gland was normal on gross and microscopic examination.

METHODS

The patients were offered weighed diets which contained little sodium, but were otherwise normal in composition. Sodium chloride was added each day with weighed salt shakers in order to raise the sodium intake to the desired level. On various occasions extra sodium chloride loads were administered intravenously as 2.5 to 5 per cent solutions. In the study of W. A., 40 mEq. of potassium chloride were added to the daily intake from the seventeenth day to the end of the study. Absolute constancy of intake was impossible in W. A. because of frequent rejections of variable amounts of salt and food; and

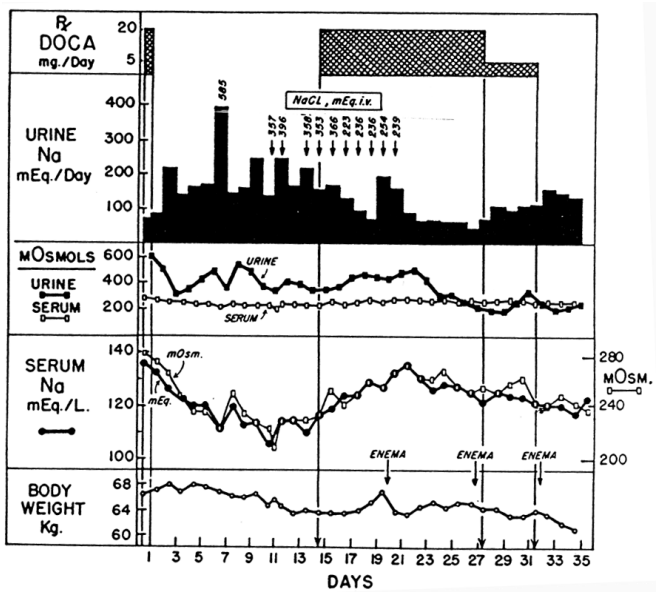

FIG. 1. Urine sodium, urine and serum osmolality, serum sodium concentration, body weight and steroid therapy during a thirty-five-day balance study of W. A. Dietary sodium intake was as follows: Days 1 to 9, 62 mEq. Days 10 to 35, 42 mEq. Supplementary sodium intake is indicated by arrows. For net intake (corrected for refusals) see Table I.

GUEST COMMENTARY

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With all due respect to my many good friends and colleagues in nephrology, I do not actually consider the 1957 paper by Schwartz *et al.* (1) to be a milestone in nephrology. This paper, which described the first cases of what would later be named the syndrome of inappropriate antidiuretic hormone secretion (SIADH), is really a milestone in medicine. The reasons justifying my opinion are several. Perhaps most important, this paper accurately described an entirely new disease syndrome that was previously unrecognized and one that is now known to be the most common cause of hyponatremia in hospitalized and ambulatory patients. Also, this syndrome is not actually a disease of the kidney itself but rather an endocrine disorder of hormone hypersecretion (which is why as an endocrinologist who studies vasopressin, the only known ADH, and its effects on the kidney, I am particularly pleased to have been asked to make these comments). But even this classification would not do justice to SIADH, because the list of potential causes of the syndrome indeed spans virtually all of internal medicine, from lung tumors as described in this original 1957 report, to a long list of systemic and central nervous system disorders. However, despite the obvious importance of describing a new syndrome, an article must be more than just a description of a new disease to be truly considered a "milestone" in any field, and my comments are focused on those aspects of this paper that amply qualify it for this designation.

First, great medical papers use insightful studies that allow a unique understanding of a previously unknown mechanism of a disease. The authors' carefully performed studies of sodium and water balance were critical for the definition of the essential characteristics of the hyponatremia seen in the two patients reported (1). Although such metabolic balance studies are decidedly low technology in this modern era of molecular biology, we can all benefit from rereading this paper to appreciate how much can in fact be learned about complex diseases from straightforward and relatively simple techniques that are applied appropriately and interpreted wisely. In addition to documenting the inappropriate kidney responses of antidiuresis and sodium excretion in the face of hypo-osmolality and hyponatremia, the authors used a series of manipulations that allowed elucidation of the underlying mechanism responsible for the hyponatremia. The demonstration that restriction of the patients' water intake resulted in weight loss and a correction of the hyponatremia (Figure 4), and conversely that water loading resulted in reinduction of the hyponatremia accompanied by weight gain and increased urine sodium excretion (Figure 5), unequivocally proved the dilutional mechanism responsible for the hyponatremia. In addition, these studies, along with the demonstration that infusion of hypertonic but not isotonic NaCl solutions corrected the hyponatremia (Figures 2 and 6), identified short- and long-term treatments

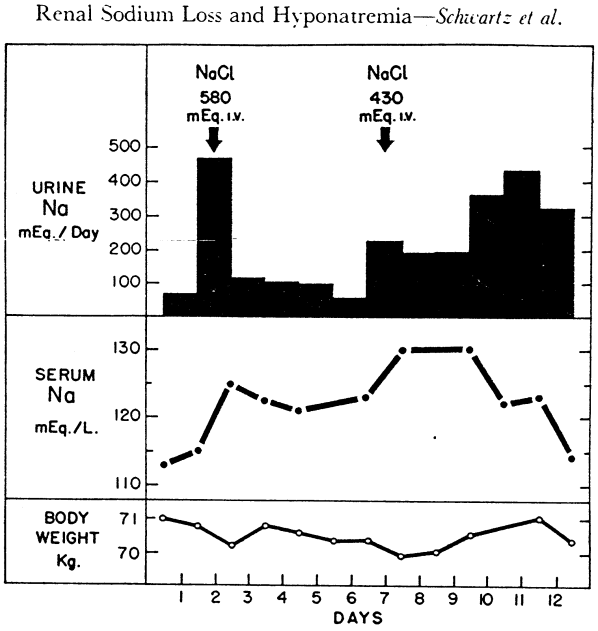

Fig. 2. Urine sodium, serum sodium concentration and body weight during a twelve-day balance study of W. F. Dietary sodium intake was as follows: Days 1 to 7, 80 mEq. Day 8, 180 mEq. Days 9 to 12, 326 mEq.

on one occasion the composition of the diet was changed. Food which was refused and vomitus were analyzed. In the studies of W. F., urinary incontinence resulted in occasional incomplete collections; losses were estimated not to have exceeded 100 cc. per day.

Measurements of inulin and p-aminohippurate clearances were made in the standard manner. The analytic procedures, the methods used in the calculations of results, and other details of the balance technic have been described previously [*2,3*]. Osmolality of the urine and blood was estimated from freezing point depression. 17-Hydroxycorticoids were measured with and without the administration of 40 units of ACTH intravenously over an eight-hour period. Urinary aldosterone was measured by a method previously described [*4*]. The radiosodium, radiosulfate and radiopotassium spaces were determined simultaneously by the method of Burrows, Hine and Ross [*5*].

RESULTS

Effects of Altering Sodium Intake. (Table 1 and Figs. 1 and 2). Patient W. A. (Table *1* and Fig. 1) was transferred from the Surgical Service, where he had been receiving large amounts of hypertonic saline solution and 10 mg. of desoxy-corticosterone acetate (DOCA) daily for three days. On the first day of the metabolic study the serum sodium concentration was 136 mEq./L. and the osmolality 282. DOCA, 20 mg., was administered on the first day and then discontinued. The patient was offered a constant diet containing 62 mEq. of sodium per day. During the first six days the serum sodium concentration fell to 108 mEq./L., and the serum osmolality to 220. During this time the urine sodium excretion rose to levels of 150 to 200 mEq. per day with a simultaneous urine osmolality of 300 to 600. The body weight at the end of this period was the same as at the beginning of the study. On day 7 the oral sodium intake was supplemented by intravenous sodium chloride to make a total of 608 mEq. On the following day the serum sodium concentration was 119 mEq./L. During the next three and a half days the serum sodium fell to 103 mEq./L. and osmolality to 202. The urine sodium ranged between 143 and 242 mEq. per

for the syndrome, which remain a mainstay of therapy for many patients with SIADH up to the present time.

Second, even the most careful of studies will not yield much insight into a disease process if interpreted incorrectly; landmark or milestone studies are generally characterized by astute and frequently groundbreaking analysis of the results and their implications. This is certainly the case with this paper. The authors' hypothesis that the paradoxical urine concentration and natriuresis they observed was "probably" (perhaps modern authors can learn a little about humility from the older literature too!) a result of inappropriate secretion of ADH was proved to be correct, at least for the vast majority of cases, by subsequent studies that used sensitive radioimmunoassays to quantify plasma arginine vasopressin levels in such patients (2). Furthermore, apropos of all high-quality clinical research, the authors' appreciation of previous experimental studies, such as those of Leaf *et al.* (3), which showed similar patterns of the kidney responses after infusions of posterior pituitary extract and water loading in normal human subjects, clearly guided their research, as well as influenced their interpretation of the results obtained.

Third, great articles generally have a sense of timelessness about them. They are not just historical landmarks but in fact can be—and are—gainfully referred to for some time in the future. There is little question that this article and the knowledge gleaned from it have admirably withstood the test of time. The criteria for the diagnosis of SIADH that evolved directly from this report (*i.e.*, hyponatremia and hypo-osmolality; continued urinary excretion of sodium; clinical euvolemia; urine concentration inappropriate for plasma osmolality; and normal renal, adrenal, and thyroid function (4)) remain the criteria by which this syndrome is defined today, almost a half-century later. Not only are our clinical diagnostic criteria identical to those elucidated through these studies, but also readers can still gain new insights from rereading the paper. For example, recent interest in the possibility of a mineralocorticoid-sensitive variant of SIADH (5) is not that surprising given the salutary responses to mineralocorticoid treatment shown in these original patients (Figure 3). And the absence of weight gain despite large decreases in plasma osmolality during some of the balance studies led to the insight that this syndrome was more complicated than simply water retention and involved critical changes in solute balance as well, although now this is thought to be related more to volume-regulatory losses of electrolytes and organic osmolytes rather than from the originally postulated inactivation of cellular solute (6). Consequently, one always learns more from reexamining a paper such as this one.

Finally, being prophetic does not harm a paper's chance of becoming a milestone either. The authors clearly noticed the parallels between their cases and other reported cases of hyponatremia and concluded, with an appropriate degree of caution, "It is possible that the hyponatremia previously reported in patients with pulmonary and central nervous disease has a similar pathologic physiology." As another example, the observation that isotonic volume expansion resulted in a hypotonic diuresis led the authors to speculate that this may represent a type of "escape" from the effects of ADH, two years before the experimental studies in animals that documented the existence of this phenomenon (7).

day and urine osmolality between 345 and 537. The body weight at the end of this period was 1.2 kg. less than at the beginning of the period. Loss of 720 cc. by vomitus contributed to this change. The blood urea nitrogen varied between 5 and 9 mg. per cent, the blood pressure remained in the vicinity of 120/70 mm. Hg, and there was no clinical evidence of dehydration. On days 10 and 11, when hyponatremia was most severe, there was nausea, one episode of vomiting, and marked irritability and aggressiveness. Even when the serum sodium concentration was as low as 103 mEq./L., large amounts of sodium were excreted in the urine and no renal sodium conservation was apparent.

When large quantities of sodium chloride were administered intravenously on days 7, 11 and 12, from one-third to one-half of the administered sodium was found in the urine during the days of infusion. The sodium balance was negative by the following day. These loads produced rises in serum sodium concentration of 2 to 11 mEq./L., the highest value attained being 119 mEq./L. There was no increase in body weight with the increases in serum sodium concentration.

Patient W. F. was given sodium chloride intravenously on two occasions while the dietary sodium intake was 80 mEq. per day (Fig. 2). On the first occasion, when 580 mEq. were administered, the serum sodium concentration rose from 115 to 125 mEq./L. More than two-thirds of the total sodium intake was found in the urine during the day of infusion, and the sodium balance was negative by the following day. Four days later when the serum sodium concentration was 123 mEq./L., the patient received an infusion of 430 mEq. of sodium chloride. The serum sodium concentration rose to 130 mEq./L. and during this day more than 40 per cent of the total sodium intake was found in the urine. Sodium balance was negative by the following day. During the subsequent four days oral sodium intake was maintained at 326 mEq. per day. The sodium balance became negative by the second day of this regimen, and the serum sodium fell from 130 to 114 mEq./L. Body weight throughout this entire twelve-day period of study remained essentially unchanged. It should be noted that the values for urinary sodium excretion are minimal figures; the determined sodium balance would have been more negative (or less positive) had there not been instances of urinary incontinence. Simultaneous urine and serum osmolality determined on many occasions consistently showed that the urine was hypertonic to the serum even when the serum osmolality was markedly subnormal. Thus while the plasma osmolality ranged from 240 to 260, the urine osmolality ranged between 390 and 590.

Summary: Both subjects showed continuous urinary sodium loss without corresponding loss of water or body weight. Despite progressive falls of serum sodium and osmolality, the urine remained continuously hypertonic to the plasma. Only transient elevations of serum sodium could be produced with large "loads" of hypertonic saline solution.

Effect of Sodium-Retaining Steroids. DOCA, 20 mg., or fluorohydrocortisone, 5 mg., high sodium intake: DOCA, 20 mg. daily, was administered to W. A. (Table I and Fig. 1) for seven days (days fifteen to twenty-one) while the sodium intake was maintained between 265 and 408 mEq. per day by the administration of additional sodium chloride intravenously, as shown in Figure 1. The urine sodium fell steadily for the first five days to reach a lower limit of 68 mEq. on the fifth day (day 19) and then rose to approximately three times this figure despite the continued administration of DOCA [*2*]. Despite this rise in sodium excretion, sodium balance remained positive throughout the seven-day period with a total positive sodium balance of

When looking back at milestones in a given field, it is useful to look ahead as well. Water metabolism—and disorders of water metabolism, such as SIADH—remains an area of ongoing intense research. Perhaps the most striking area of recent advance in our knowledge has been the discovery of the aquaporin family of water channels, which has allowed an understanding of the urinary concentration process at the cellular and molecular levels and specifically the mechanisms through which vasopressin interacts with its receptor in the collecting tubule principal cells to cause antidiuresis (8). We now know that ongoing vasopressin secretion despite the presence of hypo-osmolality, whether from ectopic tumoral secretion, as was likely in the original two cases of Schwartz *et al*., or from nonosmotic secretion from other stimuli, causes increased aquaporin-2 expression and apical membrane insertion, thereby leading to the inappropriate antidiuresis of SIADH. Conversely, the apparent escape noted by Schwartz *et al*. seems to be caused by a downregulation of the vasopressin-stimulated aquaporin-2 expression in the collecting tubules (9). Paralleling these advances in our basic knowledge of vasopressin action are emerging new therapies that will allow more efficacious treatment of SIADH via blocking the actions of vasopressin or any other antidiuretic substance on its renal receptors, thereby producing a free water diuresis, or "aquaresis," with resulting correction of hyponatremia in patients with SIADH (10); such therapeutic advances are built on the knowledge gained from clinical research studies such as this one.

We have obviously come a long way since 1957 in our understanding of water metabolism and its disorders, but this is in large part because the foundation of this field was so well established initially by the pioneering clinical research of Schwartz *et al.*, which in many ways can be considered to be one of the first milestones in this field that then set the tone for clinical and basic investigators for years to come.

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TABLE I

BALANCE DATA FOR A THIRTY-FIVE DAY STUDY OF PATIENT W. A.

			Intake					Urine									Stool				Serum						
Day	DOCA (mg./24 hr.)	Body Weight (kg.)	Fluid (cc./day)	Na (mEq./day)	K (mEq./day)	Cl (mEq./day)	N (Gm./day)	Vol. (cc.)	mOsmolality	Total mOsm./day	Na (mEq./day)	K (mEq./day)	Cl (mEq./day)	N (Gm./day)	NH_4 (mEq./day)	Titratable acidity (mEq./day)	Na (mEq./day)	K (mEq./day)	Cl (mEq./day)	N (Gm./day)	pH	CO_2 (mEq./L.)	Na (mEq./L.)	K (mEq./L.)	Cl (mEq./L.)	BUN (mg./100 cc.)	mOsmolality
1	20	66.60	2946	62	100	83	9.0	920	602	554	72	37	127	5.4	63	9.0	7	17	9	10.0	....	....	136	4.1	105	..	282
2	.	67.06	2821	59	95	80	8.3	1200	510	612	86	47	144	6.1	61	9.8	7	17	9	10.0	7.46	27.7	133	3.7	100	8	272
3	.	68.08	2946	62	85	83	8.5	2500	309	773	213	37	185	5.8	38	0	7	17	9	10.0	7.48	28.6	128	3.7	90	8	267
4	.	66.77	2946	59	85	80	8.3	1600	350	560	142	21	101	5.0	23	0	7	17	9	10.0	7.51	27.4	121	3.7	86	..	249
5	.	67.85	2906	59	100	80	8.8	1420	428	608	167	42	109	6.5	12	0	7	17	9	10.0	7.50	25.8	120	4.5	88	7	236
6	..	67.59	2946	59	100	80	8.8	1720	493	848	170	82	147	6.4	11	0	7	17	9	10.0	7.40	22.7	120	4.2	89	8	238
7	..	66.66	3846	608	51	614	4.4	3449	360	1242	393	90	128	8.1	50	11.0	7	17	9	10.0	7.46	24.3	108	4.4	81	8	220
8	..	66.24	2126	30	50	41	4.8	950	537	510	143	36	151	4.7	23	2.3	7	17	9	10.0	7.44	23.0	119	4.5	93	7	248
9	..	66.09	2946	43	83	62	7.3	1318	478	630	160	66	161	5.5	17	0	7	17	9	10.0	7.47	22.6	112	4.8	85	5	235
10*	..	66.36	2195	22	32	28	7.1	2320	363	842	242	69	197	7.4	26	0	7	17	9	10.0	7.47	22.8	113	4.5	80	6	227
11†	..	64.73	1705	0	0	0	0	1095	345	378	86	26	64	3.7	15	0	7	17	9	10.0	7.49	22.4	105	4.4	80	6	220
		65.43	410	357	0	357	0	640	333	213	49	13	39	2.6	17	0	..	..	..	....	....	....	103	....	....	..	202
12	..	64.10	2551	396	20	416	0	2083	401	835	211	42	248	6.7	48	7.3	7	17	9	10.0	7.48	20.9	113	4.1	86	7	230
13	..	63.63	2979	7	32	13	7.1	1765	391	690	162	33	199	6.4	51	5.1	7	17	9	10.0	7.49	21.1	115	4.3	90	9	231
14	..	63.85	3031	359	8	361	1.5	2360	345	814	212	36	239	7.3	59	0	7	17	9	10.0	7.50	22.5	109	4.1	83	8	227
15	20	63.53	2980	360	32	366	7.1	2110	332	701	154	46	233	6.3	67	16.5	7	17	9	10.0	7.49	21.7	115	3.9	87	6	230
16	20	63.31	2943	108	32	413	7.1	2037	350	713	169	43	217	6.3	69	11.4	7	17	9	10.0	7.50	22.8	118	2.8	93	5	250
17	20	63.33	2946	265	81	322	7.1	1560	446	696	131	41	221	7.2	85	15.3	7	17	9	10.0	7.50	21.1	123	3.3	98	6	238
18	20	64.07	2941	278	94	345	7.1	1110	456	506	91	10	153	5.4	44	7.7	7	17	9	10.0	7.51	24.4	121	3.0	99	7	251
19	20	65.00	2982	278	99	350	7.1	875	435	381	68	39	120	4.3	31	7.9	7	17	9	10.0	7.50	24.1	129	3.2	100	8	258
20‡	20	66.55	1558	296	64	333	7.1	1980	415	822	193	86	287	6.9	52	16.4	7	17	9	10.0	7.52	24.9	128	3.1	98	8	255
21	20	63.65	1863	281	67	321	7.1	1510	470	710	161	78	237	6.2	42	17.7	3	7	3	0.7	7.50	25.5	132	3.1	102	9	268
22	20	63.29	3052	42	72	87	7.1	1030	490	505	84	61	142	5.7	38	17.8	3	7	3	0.7	7.52	26.5	135	3.0	104	9	271
23	20	64.16	2800	42	72	87	7.1	1420	415	589	66	72	131	8.5	47	21.2	3	7	3	0.7	7.51	26.4	130	3.0	100	9	262
24	20	64.96	2325	42	72	87	7.1	2025	278	563	67	77	121	8.0	43	15.2	3	7	3	0.7	7.53	25.7	125	2.7	95	13	258
25	20	64.41	3060	42	76	87	6.4	1900	291	553	61	75	112	8.3	48	14.3	3	7	3	0.7	7.57	26.3	127	2.9	94	12	260
26	20	64.80	3085	42	76	87	6.4	2120	254	538	63	78	115	7.4	53	9.3	3	7	3	0.7	7.49	25.2	127	2.6	96	7	256
27†	20	64.94	3070	42	76	87	6.4	2042	198	404	44	58	88	5.5	49	9.0	3	7	3	0.7	7.52	26.9	125	2.6	94	10	250
28	5	64.32	3070	42	76	87	6.4	2675	178	476	68	60	108	5.6	54	8.6	3	7	3	0.7	7.51	25.6	121	2.3	94	8	248
29	5	64.15	3070	42	72	87	7.1	3540	167	591	106	55	138	6.0	53	9.6	3	7	3	0.7	7.52	26.2	123	2.6	92	6	247
30	5	63.22	3070	12	72	87	7.1	2475	213	527	96	53	116	5.7	50	7.1	3	7	3	0.7	7.52	26.2	124	2.6	97	6	250
31‡	5	63.13	3070	39	62	83	4.1	1720	311	535	107	67	124	5.2	40	5.8	3	7	3	0.7	7.52	25.5	122	2.8	90	8	248
32	..	63.84	3070	35	61	80	4.1	2615	215	562	108	10	124	4.3	52	6.3	3	7	3	0.7	7.52	23.7	119	2.8	87	8	239
33	..	63.16	3070	12	72	87	7.1	3425	178	610	156	41	151	7.9	39	5.8	3	7	3	0.7	7.53	24.5	120	3.0	86	7	238
34	..	62.96	3070	12	72	87	7.1	2788	195	544	113	37	126	5.0	34	4.5	3	7	3	0.7	7.51	25.0	119	3.4	87	7	240
35	..	61.30	3070	12	72	87	7.1	2110	200	482	134	42	123	4.7	28	4.3	3	7	3	0.7	7.53	21.6	115	3.6	87	6	237
36	..	61.06	....	....	....	....	....	....	....	....	....	..	....	....	..	....	..	..	..	....	7.50	21.3	117	4.1	87	..	240

* Additional volume loss of 720 cc. vomitus, 7.8 mEq. Na, 9.4 mEq. K, 20.6 mEq. Cl, 1.5 gm. N.
† Additional volume loss of 385 cc. vomitus, 8.6 mEq. Na, 5.3 mEq. K, 35.4 mEq. Cl, 0.3 gm. N.
‡ Enema given on this day.

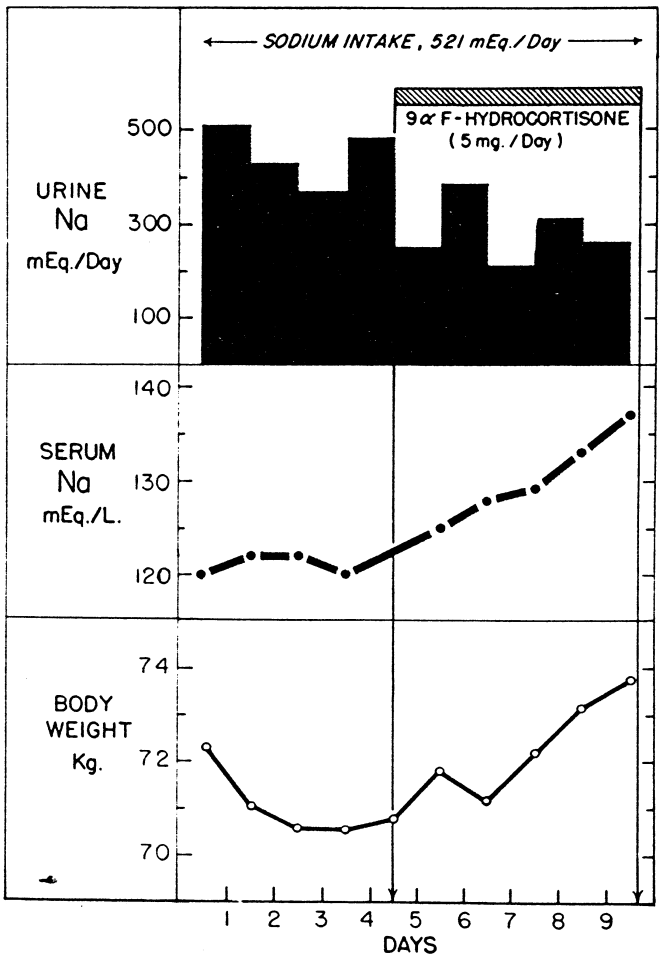

FIG. 3. Urine sodium, serum sodium concentration, body weight and steroid therapy during a nine-day study of W. F.

1.154 mEq. The urine osmolality ranged between 332 and 470. During this time the serum sodium concentration rose from 115 to 135 mEq./L. and serum osmolality from 230 to 271. The body weight rose during the first five days by a total of 3 kg. and then fell abruptly to the initial level. This weight loss was attributable to removal by enema of a large quantity of feces which had been accumulating throughout the entire study. The serum potassium fell from 4.1 mEq./L. to 2.3 mEq./L. during administration of DOCA, and returned to the initial level after DOCA was stopped. Hydrogen ion excretion, as estimated from urine ammonium and titratable acidity, rose when DOCA was administered, and fell again when it was discontinued.

Fluorohydrocortisone, 5 mg. daily, was administered to W. F. (Fig. 3) after a preliminary four-day period during which his serum sodium concentration had been maintained at levels of approximately 120 mEq./L. by daily administration of 520 mM. of sodium chloride. On this medication the serum sodium concentration rose in stepwise fashion to 137 mEq./L., and the body weight rose by 3 kg. Urine sodium fell to approximately half of the control values, indicating sodium retention of approximately 1,000 mEq. during the treatment. The actual figure may have been somewhat less, because there were small losses of urine, estimated to be less than 5 per cent of the average daily volume. The study was discontinued because of severe hypokalemia.

DOCA, 20 mg., low sodium intake (Table I *and Fig. 1):* DOCA in a dose of 20 mg. daily was given to patient W. A. for an additional six days (days twenty-two to twenty-seven), with a sodium intake of 42 mEq. daily. The urine sodium fell abruptly with institution of the low sodium regimen but did not become as low as the intake until the sixth day. There was a total negative sodium balance of 151 mEq. during this six-day period. Urine osmolality fell from 490 to 198. During this time the serum sodium concentration fell from 135 mEq./L. to 121 mEq./L. and serum osmolality from 271 to 248. The body weight rose a total of 1 kg. during this six-day period.

DOCA, 5 mg., low sodium intake (Table I *and Fig. 1):* DOCA, 5 mg. daily, was given to W. A. for four days (days twenty-eight to thirty-one) together with a sodium intake of 42 mEq. per day. The urine sodium rose to approximately 100 mEq. per day. There was a total negative sodium balance of 224 mEq. Urine osmolality ranged from 167 to 311. The serum sodium concentration was 121 mEq./L. at the beginning and 119 mEq./L. at the end of the period. Body weight fell 0.5 kg.

Withdrawal of DOCA (Table I *and Fig. 1):* DOCA was withdrawn from patient W. A. (Table I, Fig. 1) and the effects observed for a four-day period (days thirty-two to thirty-five) with a dietary sodium of 42 mEq. per day. The urine sodium excretion rose further, and there was a total negative balance of 392 mEq. The urine osmolality ranged from 178 to 215. The serum sodium concentration was 119 mEq./L. at the beginning and 117 mEq./L. at the end of the period. Body weight fell by 2.8 kg.

Summary: Both subjects responded to salt-retaining steroids with normal sodium retention. The serum sodium concentration and body weight rose.

Effect of Changes in Fluid Intake (Figs 4, 5 and 6.) Three months after the initial metabolic studies, W. A. (Fig. 4) was admitted to the hospital for study of the effects of dehydration on electrolyte excretion. He was given a daily water intake of approximately 2,000 cc., a value about twice that which he had been taking, and approximately 10 mEq. of sodium. After a three-day control period he was subjected to dehydration for six days and then a liberal intake of fluid was resumed. During the first three days, when the fluid intake was liberal, the patient's urine sodium varied between 75 and 109 mEq. per day, and urine osmolality between 490 and 641. The serum sodium concentration decreased from 127 to 114 mEq./L. Body weight did not change significantly. With dehydration the urine sodium decreased steadily to a minimum value of 6 mEq. per day. During the afternoon and evening the first day of dehydration, 290 mEq. of sodium chloride were given intravenously as a 5 per cent solution. In contrast to the very large sodium diuresis produced by similar procedures previously, the sodium excretion fell to 36 mEq. per day. The serum sodium concentration rose from 114 to 123 mEq./L., and during the next five days increased to 135 mEq./L. The body weight fell by 4.9 kg. With rehydration, the urine sodium rose progressively as the serum sodium fell. Body weight rose by 2.6 kg. On the third day 56 mEq. of sodium was excreted on an intake of 10 mEq. When sodium loads were given after rehydration (Fig. 4, days thirteen and fifteen), there were again large increases in urinary sodium. The blood urea nitrogen showed a transitory rise during dehydration.

In W. F. (Fig. 5) after the fluid intake had been 2,000 cc. per day for a two-week period, with maintenance of a normal serum sodium concentration and an essentially constant body weight, the fluid intake was increased to 3,000 cc. per day. There promptly followed a marked rise in urinary sodium excretion to figures greater than the intake (140 mEq. per day), and a fall in serum sodium concentration from 142 mEq./L. to 120 mEq./L., while body weight rose 2 kg.

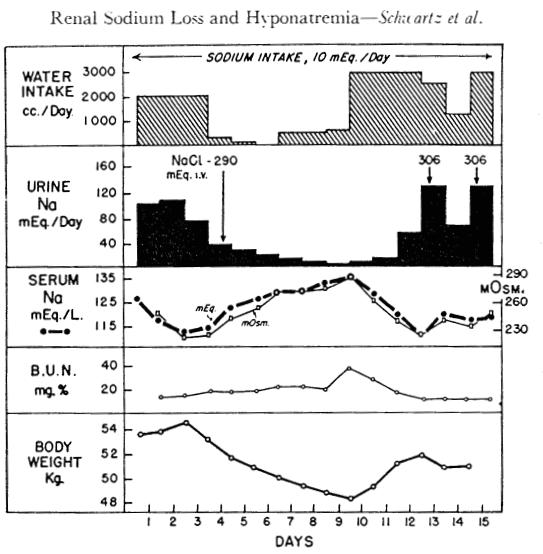

FIG. 4. Fluid intake, urine sodium, blood urea nitrogen, serum sodium and osmolality, and body weight during a fifteen-day study of W. A. Supplementary sodium intake is indicated by arrows.

W. A. was subjected to a rapid expansion of extracellular fluid by the administration of 2,000 cc. of sodium chloride solution intravenously over a two-hour period, at a time when his serum tonicity was subnormal (sodium 116 mEq./L., 234 mOsm.). (Fig. 6.) The concentration of sodium in the infusion was 142 mEq./L. This was sufficient to raise the serum sodium and osmolality by small but significant amounts during the infusion. The procedure resulted in a rise in urine flow from between 1 and 2 cc. to 17 cc. per minute. Urine osmolality fell progressively from 449 to 151 and the osmolar U/P ratio from 1.75 to 0.60. Concomitantly the sodium excretion rose from initial values of approximately 100 μEq./minute to 1,000 μEq./minute at the height of the diuresis.

Summary: In both subjects fluid restriction led to sodium retention and a return of the serum sodium concentration to normal. Restoration of liberal fluid intake re-established the sodium-losing syndrome. One subject was given a rapid infusion of saline hypertonic to his plasma; this was followed promptly by a reduction in urine osmolality to values below those of the plasma, with copious diuresis.

"Space" Estimations. Radiosulfate, radiosodium and radiopotassium spaces: On day nine (Fig. 1), when the serum sodium concentration was 112 mEq./L., radiosulfate, radiosodium and radiopotassium spaces were determined in W. A. The twenty-minute radiosulfate and radiosodium spaces were 17.2 and 17.3 L. respectively, a volume of distribution equal to about 26 per cent of body weight. These values are approximately 50 per cent greater than those obtained in normal subjects by these methods [*6,7*]. At twenty-four hours the "total body sodium" exchangeable with the isotope was estimated at 2,388 mEq. or 36.3 mEq./kg This value is approximately 25 per cent below that obtained in normal subjects by this method. If, however, the sodium which had been lost by the patient during the time his serum sodium was falling from normal levels be added to it, then the "corrected" total body sodium is normal (44.8 mEq./kg.). At twenty-four hours the "total body potassium" exchangeable with the isotope was estimated at 2,193 mEq. or 33.3 mEq./Kg. This value is approximately 25 per cent below that obtained in normal subjects by this method. Even when the apparent expansion of extracellular fluid volume is taken into consideration, the corrected per kg. value remains below normal.

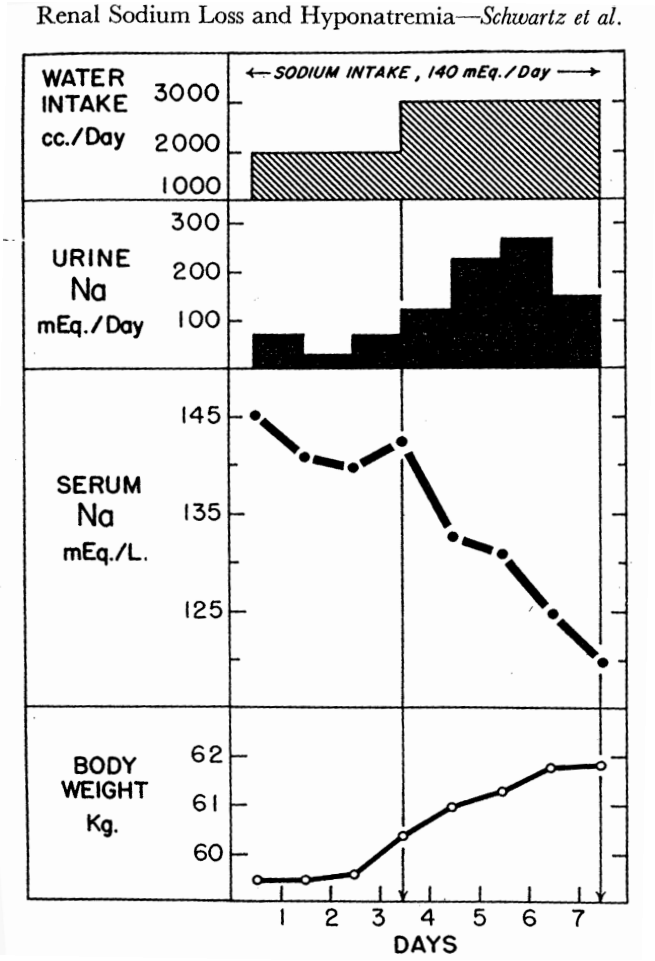

FIG. 5. Fluid intake, urine sodium, serum sodium concentration and body weight during a seven-day study of W. F. Minimum osmolality of urine (based on 2 × [Na] + [K]) ranged from 280 to 440 on days 4 through 7.

"Chloride space" changes: From the data in Table I, chloride spaces were calculated for W. A. They showed (1) a net decrease of 0.3 L. during metabolic days 1 through 6 (Fig. 1) before administration of any salt loads, (2) a net decrease of 0.4 L. during metabolic days 1 through 9, which included a salt load on day 7, (3) an increase of 5.7 L. during metabolic days 15 through 21 when DOCA was administered with a high salt intake, (4) a decrease of 0.2 L. during metabolic days 22 through 31 when DOCA was given with a low salt intake, and (5) a decrease of 2.3 L. during metabolic days 32 through 35 after DOCA was discontinued.

Summary: The extracellular fluid volume appeared to be substantially above normal in the one subject in whom it was estimated. In this subject, chloride space did not decrease significantly as hyponatremia developed but increased markedly during administration of DOCA.

Adrenal Function. The clinical findings relevant to adrenal function were as follows: There was no abnormal pigmentation, axillary and pubic hair were normal, and blood pressure was normal in one subject and persistently high in the other. Even with severe hyponatremia, there was no evidence of dehydration, blood pressure remained unchanged, and there was no fever, diarrhea or rise in serum potassium concentration. In both patients (*vide supra*) a normal serum sodium concentration could be maintained for extended periods by simple fluid restriction with low or moderate sodium intake.

In W. A., circulating eosinophils fell from 700 to 187 after eight hours of administration of ACTH; twenty-four-hour uri-

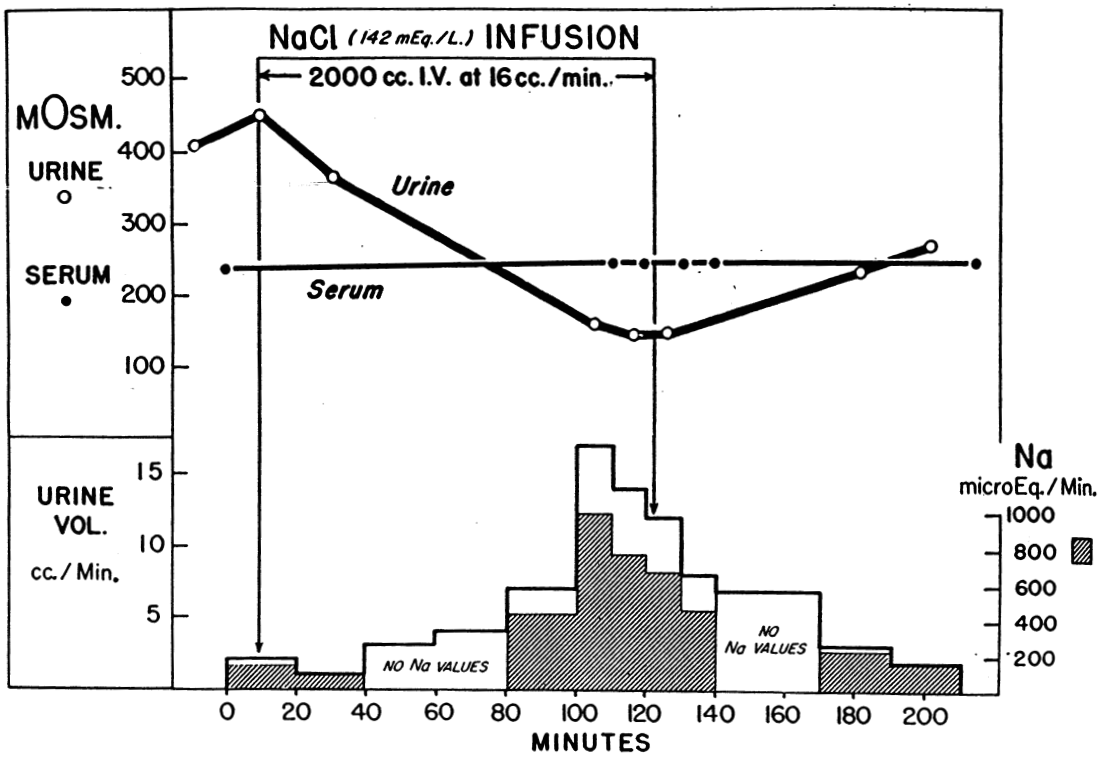

FIG. 6. Urine and serum osmolality, urine volume and urine sodium excretion during the rapid infusion of "normal" saline solution to W. A.

nary 17-hydroxy-corticoids rose from 6.4 to 12.7 mg. Aldosterone excretion was measured twice on low and twice on high sodium intakes while the serum sodium concentration ranged from 103 to 115 mEq./L., and showed a range from 3 to 5 μg. per day. In W. F., circulating eosinophils fell from 188 to 13 after eight hours of administration of ACTH; plasma 17-hydroxycorticoids rose from 8 to 35 μg. per 100 cc., and twenty-four-hour urinary 17-hydroxycorticoids rose from 9 to 22 mg. Aldosterone excretion was measured on a normal sodium intake (80 mEq. per day), while the serum sodium concentration was 120 mEq./L., and was found to be 5 μg. per day.

The pathologic findings (*vide supra*) showed normal adrenal cortices in the subject who died shortly after the studies were completed, and extensive invasion of the adrenal cortices in the other who died eight months after the studies were made.

Summary: Both subjects showed normal adrenal cortical function as judged from clinical and biochemical evidence.

Renal Function: The urine was normal on numerous occasions in both subjects, as was the blood urea nitrogen. In W. A. the inulin clearance was 120 cc./minute and the p-amino-hippurate clearance 694 cc./minute, when the serum sodium concentration was 108 mEq./L. In W. F. the inulin clearance was 170 cc./minute and the p-aminohippurate clearance 650 cc./minute, when the serum sodium concentration was 124 mEq./L.

The pathologic findings (*vide supra*) showed that the kidneys were normal both grossly and microscopically except for scattered metastases in one subject and minor arteriosclerotic changes in both.

Summary: Both subjects showed normal renal function as judged from urinalyses, glomerular filtration rates and renal plasma flows.

COMMENTS

These two patients with mediastinal tumors presented a syndrome in which the cardinal feature was hyponatremia. Renal and adrenal cortical function was normal. As hyponatremia and hypotonicity of the extracellular fluid developed, the urine was persistently hypertonic to the plasma. According to current concepts, hypertonicity of the urine, in the presence of a normal glomerular filtration rate, constitutes *prima facie* evidence for the presence of anti-diuretic hormone (ADH) [*8–10*]. It is postulated that there was sustained, inappropriate secretion of ADH in these subjects, and that this was responsible for the disorder of sodium metabolism. When pitressin and abundant fluids are given continuously to normal subjects a similar pattern of hyponatremia with persistently concentrated urine also is observed [*11*]. Normal subjects treated in this fashion* exhibit negative sodium balance, as did the patients in the present study [*11*]. When, on the other hand, pitressin is given continuously to normal subjects and fluid intake is restricted, hyponatremia and urinary sodium loss do not occur; similarly, sodium loss ceased and serum sodium concentration rose to normal values when the patients' fluid intake was restricted.

The production of ADH in these subjects could not have been governed by normal osmo-regulatory mechanisms [*13*], since it persisted in the face of progressive reduction in the tonicity of the plasma. Reduction of extracellular fluid volume may lead to elaboration of an hypertonic urine, possibly via the secretion of ADH [*14*]. There was no clinical evidence of dehydration in the subjects reported here. Indeed, the values for the twenty-minute radiosulfate and radiosodium spaces indicated that the extracellular fluid volume in W. A. was increased at a time when the serum sodium concentration was far below normal. In the absence of any known stimulus to ADH production, it appears likely that its continued inappropriate secretion was a result of the disease process.

It is unlikely that the continued production of ADH in these subjects represented a lowered threshold for stimulation of osmoreceptors (such as might result from primary reduction of

*Normal subjects given pitressin while unaware of the nature of the medication and offered water *ad libitum* continued to drink water in sufficient quantities to develop and maintain a severe sodium-wasting syndrome with progressive hyponatremia for as long as two weeks [*12*].

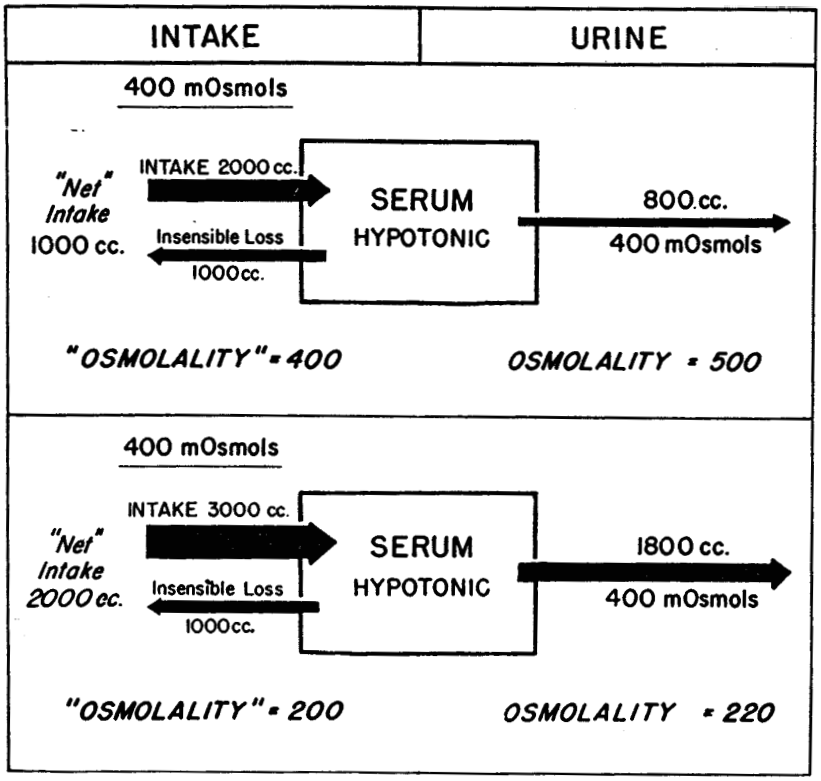

FIG. 7. Diagram to illustrate the production of serum hypotonicity despite urine osmolality below that of plasma. Both subjects are shown as accumulating 200 cc. per day.

the osmolality of cells), since hypertonicity of the urine persisted in spite of a plasma osmolality as low as 202. The response to sodium-retaining steroids furnishes further evidence that the hypotonicity was probably not a result of a very low "setting" of an osmoregulator controlling the secretion of ADH. If this were the case the sodium retained on steroid therapy should, by producing hypertonicity of body fluid relative to this setting, lead to further output of ADH and further water retention, thus maintaining the hypotonic state. In these subjects, however, serum tonicity rose markedly with steroid therapy, and the urine did not even approach its maximum osmolar concentration.

It should be noted that it is not necessary that the urine be hypertonic to the plasma in order that the tonicity of the serum fall below normal or be maintained at subnormal levels; it is essential only that the "osmolality of the total intake" be lower than or equal to that of the urine.* (Fig. 7.) Indeed, all available evidence indicates that when the urine is not maximally dilute, this alone, in the presence of a normal glomerular filtration rate, constitutes evidence for the continued presence of ADH.

When W. A. was subjected to a rapid expansion of his extracellular fluid with saline slightly hypertonic to his serum, there ensued a copious diuresis of hypotonic urine (17 cc./minute with osmolar U/P .61). A response such as this to expansion of body fluid volume may explain the failure of these subjects to retain water indefinitely. It is likely that a critical expansion of volume would be reached spontaneously which would set in operation a similar train of events. It is not certain from the evidence at hand whether this phenomenon is the result of a decrease in the production of ADH or represents an "escape" from ADH such as that described in normal subjects given mannitol during constant infusions of pitressin [*15*].

During days 1 through 6 of the metabolic study in W. A. there was no weight change and the serum osmolality fell by 62. If it is assumed that osmotic equilibrium is maintained between intracellular and extracellular fluid, and that total body water is not less than 50 per cent of the body by weight, this implies the removal of approximately 2,000 mOsmol. during the six-day period. In fact, there was a slightly positive potassium balance during this period and the negative sodium and chloride balance accounted for only about 1,000 mOsmol. The hazards inherent in the rigid interpretation of cumulative metabolic data are well recognized, but this "osmotic" discrepancy appears to be significant even after liberal allowances are made for skin loss. A similar calculation for the period ending on day 11 gives comparable results. It follows, therefore, if our assumptions are correct, that progressively larger amounts of intracellular solute must have become osmotically "inactive" as the serum tonicity decreased. Whether this was a result or could possibly have been a cause of the inappropriate secretion of ADH postulated here cannot be determined from the information at hand.

During the first six days the fall in serum osmolality would have been expected to result in a gain of approximately 9 L. of intracellular water. However, as there was no increase in body weight, intracellular dilution could not have resulted from a positive water balance. There was no clinical or laboratory evidence that significant amounts of fluid had shifted from the extracellular to the intracellular space. The chloride space did not change, and the radiosodium and radiosulfate determinations showed an abnormally large extracellular volume. The blood pressure did not fall, there were no symptoms suggestive of vascular collapse, and the glomerular filtration rate was normal. One is therefore forced to the conclusion that, as suggested, intracellular solute had become osmotically "inactive."

*The "osmolality of the total intake" is here taken to mean the osmolality of an hypothetic solution in which all the actual and potential solute particles in the diet destined for urinary excretion are dissolved in an amount of fluid equal to that in the diet (including water of oxidation) minus that of the "insensible loss".

Weight gain did not occur in either subject when the serum sodium concentration was raised with hypertonic saline solution. When, in contrast, the serum sodium concentration rose as the result of increased tubular reabsorption of sodium produced by steroids, body weight increased and the urine volume decreased. It is unlikely that the water retention with the steroids can be attributed to increased secretion of ADH in response to the rise in serum osmolality [*13*], as in that case it should have occurred with hypertonic saline solution as well. Furthermore, the ADH output in these patients appeared in all other respects to be independent of serum tonicity. If the action of ADH is to allow a dilute tubular urine to become isotonic with plasma at a distal site [*10,16*], then a steroid-induced increase of sodium reabsorption proximally thereto might be expected to allow it to induce more water reabsorption.

After the serum sodium had been raised by infusion of hypertonic saline solution, weight loss did not occur in either subject during the subsequent spontaneous fall in the serum sodium concentration. When steroid therapy was discontinued, however, loss of weight accompanied the sodium loss. The tonicity of the urine fell. This phenomenon may be in part a reversal of the one discussed. It is likely, however, that it represents also a response to overexpansion of the extracellular fluid, exactly analogous to that produced when W. A. was given an infusion of sodium chloride (Fig. 6.). It should be noted (Fig. 1) that the loss of sodium and water began even before DOCA was discontinued, at a time when the chloride space showed an expansion of 5.7 L. A similar escape from the influence of DOCA has been described for normal subjects [*2*].

These studies do not explain the mechanism whereby continued inappropriate secretion of ADH might have been produced in these patients. Each patient had a mediastinal tumor, and it may be that the stimulus arose as a result of a direct effect on some intrathoracic structure, such as the vagus nerves [*17*]. Each patient also had brain disease, and this may have served in some fashion to produce continued secretion of ADH. The mechanism by which inappropriate ADH in turn allows sodium loss probably involves (1) an increase of glomerular filtration rate [*3*] and (2) a failure of aldosterone secretion to rise as it would from the volume contraction which ordinarily accompanies sodium depletion [*3*].

Asymptomatic hyponatremia with appreciable sodium in the urine has been reported in patients with pulmonary tuberculosis and meningitis [*18–21*] and in one patient with bronchogenic carcinoma [*18*]. These patients resembled those reported here in showing no dehydration, vascular collapse or nitrogen retention as the serum sodium fell. In fact, normal to high extracellular fluid volumes have been observed in patients with hyponatremia and tuberculous meningitis [*21,22*]. Patients with so-called asymptomatic hyponatremia previously reported on differ from our subjects in that their serum sodium concentration tended to stabilize at moderately reduced levels. It is possible that the mechanism whereby hyponatremia was produced and maintained in some of the reported cases was related to that in our two patients, but critical data bearing on this point are not available.

SUMMARY AND CONCLUSIONS

Studies are reported on two subjects with bronchogenic carcinoma who had marked progressive hyponatremia with urinary sodium loss, despite normal renal and adrenal function. The urine was persistently hypertonic to the plasma, and contraction of body fluid volume did not occur as sodium depletion and hypotonicity of the plasma progressed.

It is postulated that the underlying disease process induced in some manner a sustained, inappropriate secretion of antidiuretic hormone, and that the syndrome was a consequence of the resultant expansion of body fluid volume.

All the essential features have been produced in normal subjects by continuous administration of pitressin and water. As with the normal subjects, restriction of fluids in the patients reported here prevented sodium loss and hyponatremia.

It is possible that the hyponatremia previously reported in patients with pulmonary and central nervous disease has a similar pathologic physiology, but critical data to settle this question are not available.

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