Inappropriate Antidiuresis: Examples of an Hyponatremic Syndrome Resembling Exogenous Vasopressin Administration in Man

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Hyponatremia has been recognized as a clinical entity since the finding by Loeb in 1932 that significantly lowered serum sodium and chloride levels are a characteristic finding in Addison's disease. It soon became apparent with the work of Winkler and Crankshaw in 1938, that hyponatremia was an accompaniment of diverse disease states as repeatedly confirmed since the introduction and clinical application of flame photometry for sodium analyses (Berry, Chappell, and Barnes, 1946; Fox and Baer, 1947; Hald, 1947; Bowman and Berliner, 1949; Wallace et al., 1951). Early papers emphasized the occurrence of hyponatremia in the two broad categories of cerebral and pulmonary disease (Peters et al., 1950; Sims et al., 1950; Welt et al., 1952; Cort, 1954); additional reports indicated a frequency of occurrence in tuberculous meningitis (Rapoport, West, and Brodsky, 1951; Harrison, Finberg, and Fleischman, 1952; Cheek, 1956; Arblaster and Whitehead, 1957). Despite the renal sodium loss in these patients under certain circumstances, evidence indicates that primary water retention is present upon one or another bases in most cases of hyponatremia (Fuisz, 1963). In recent years cases have been described in which this clearly appears to be mediated by continuous antidiuretic activity. Whether or not these cases for the most part represent failure of physiologic control or inactivation of pituitary antidiuretic hormone (vasopressin), with abnormal biosynthesis of substances possessing vasopressin activity being importantly implicated in cases of bronchogenic carcinoma, is an issue that needs clarification. This report deals with clinical illustrations of this syndrome, and with special physiological studies pertinent to the underlying mechanisms.

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Case Histories

Case 1, C.G. A 49-year-old carpenter entered the MCV hospital because of a left hilar density seen on a chest roentgenogram. Following an episode of pneumonia 13 months before admission he had frequent upper respiratory infections and was aware of progressive malaise with 17-pound weight loss. Sputum was blood-streaked on a few occasions. He had smoked one pack of cigarettes per day for more than 25 years. On physical examination he was without complaint and appeared to be well-nourished; his weight was 59 kg and his height, 167 cm. Breath sounds were diminished posteriorly on the left from the inferior border of the scapula to the base. The liver was not enlarged. The pulse was 88 per minute and the blood pressure 155/80 mm Hg. Neurologic examination was normal. Chest film showed a nodular left hilar density 4 cm in diameter. Hemoglobin was 13 g/100 ml; white cell count was 10,200/mm^3 with a normal differential count. Serum sodium concentration was 125 mEq/L, K, 3.8; Cl, 88 and bicarbonate 23 mM/L. Blood urea nitrogen (BUN) was 8 mg/100 ml. Alkaline phosphatase was 3.41 Bessey-Lowry units. Other blood studies including calcium, phosphorous, total protein, albumin, GO transaminase, bilirubin and Bromsulphalein were normal. Admission urine specific gravity was 1.012 and was not otherwise remarkable. Skull roentgenogram and bone survey for metastatic disease showed no pathologic changes. Bilateral scalene node biopsies revealed chronic lymphadenitis without tumor; bronchoscopy failed to reveal a lesion. Arterial hemoglobin-oxygen saturation was 92%.

Five days after admission serum sodium was 128 mM/L and two days later, it was 118 mM/L. By then the patient complained of constant severe headache. Serum osmolality was 236 mOsm/kg, while urine osmolality was 316 mOsm/kg. Twenty-four-hour urine 17-hydroxy- and 17 keto steroid values were normal, with a normal rise after 50 units ACTH on two successive days. Urea N was less than 7 mg/100ml. Urine culture was negative. At this point the procedures detailed under "Special Studies" were begun. During the course of this study

the patient exhibited bizarre behavior associated with serum sodium values below 110 mEq/L, and with values approaching 100 mEq/L, he developed vomiting and pain in the abdomen. These symptoms subsided with rise of sodium values toward normal associated with moderate water restriction and a 9-α-fluorohydrocortisone administration. Right carotid arteriogram, performed because of the persistent headache, failed to show filling of the right middle cerebral artery; electroencephalogram revealed only mild generalized slowing. Coincident with improvement of the patient's cerebral symptoms, his liver became palpable. Repeat bronchoscopy revealed a lesion of the left main stem bronchus which was biopsied. Open biopsy of the liver was carried out to determine the advisability of thoracotomy for definitive removal of the tumor. Biopsies from each site showed poorly differentiated bronchogenic carcinoma of the oat cell type. Subsequently the patient developed a left pleural effusion in addition to suspected obstruction of the left main bronchus. The patient died three weeks later.

Autopsy revealed extensive neoplastic involvement of the lower lobe of the left lung with occlusion of the left main bronchus and distal atelectasis. The tumor was identified as poorly differentiated bronchogenic carcinoma, oat cell type, with extensive metastases involving lung tissue; several small nodules of metastatic tumor were found in the adrenals, and on the left there was a small encapsulated cortical adenoma. The kidneys were normal. Gross and microscopic examination of the brain revealed no abnormality. A tiny focus of fibrous tissue containing dilated vessels was seen in the anterior pituitary, but comprised only a small portion of the parenchyma. The posterior pituitary was normal.

Case 2, W.M. The patient, aged 42, fell out of a tree on September 19, 1961, landing feet first, but fell to the ground and was knocked unconscious. He was transported to a nearby hospital, where he regained consciousness, and was found to have suffered dislocation of a cervical vertebra. Head halter traction was instituted immediately, and three days later, he was transferred by ambulance to the neurosurgical service of the V.A. Hospital, Richmond. Upon admission he was mentally clear and complained of moderate pain in the neck and right shoulder. There was no deformity of the neck and no external evidence of injury of the head. Blood pressure was 136/90. There was a right nephrectomy scar dating from 1946. There was no loss of strength or changes in reflexes in any of the extremities, and no loss of bowel or bladder continence. X-rays revealed 40% anterior displacement of C4 or C5, with obliteration of the interspace, but no fracture line was visualized. X-rays of the skull and the right shoulder girdle also were normal. BUN was 15 mg/100 ml; fasting blood sugar, 77 mg/100 ml, and hematocrit, 42%.

On October 17, he was noted to be confused, disoriented, and partially aphasic. There was no peripheral motor or sensory change. BUN was 11 mg/100ml and Hct, 32%. Carotid arteriogram was normal. He remained afebrile. Left temporal and right frontal trephinization and ventriculography were done to rule out subdural hematoma. On October 23, BUN was 9 mg/100 ml, and on the following day, 8 mg/100 ml. Serum Na was 109, Cl 77, K 4.3, and bicarbonate, 21 mEq/L. On each of the three preceding days he had received parenteral fluids. He now had left facial twitching, refused food, and remained confused. Parenteral fluids were discontinued because he was considered well hydrated, and in the following week his mental state improved. On October 31, serum Na was 113, Cl, 81, and K, 5.2. On November 1, he was placed in a jacket cast, traction was discontinued, and he was allowed out of bed. He alternated between euphoria and confusion, but was no longer uncooperative. On January 3, 1962, a small fragment of parietal skull involved with osteomyelitis was removed under local anesthesia. On January 15, 1962, he was transferred for investigation of hyponatremia. Results are detailed in the section on special studies.

Case 3, W.F. The patient, aged 50, entered the V.A. Hospital on October 18, 1962, complaining of intermittent fever (101° to 102°) for five months, associated with severe bilateral occipital headaches, recurrent vomiting, diffuse myalgias, and progressive generalized weakness. He had been treated by his local physician with penicillin and tetracycline with remission of these symptoms, except that emesis had progressed to a frequency of four to five times daily. He had had no hematemesis, no alteration of bowel habits, and there had been no nuchal rigidity, scotomata, diplopia, or dysphagia. He had had one episode of mental confusion several weeks before admission and had recently noted episodic dizziness and unsteadiness of gait. One year before admission he had had a tender swollen right knee, yielding purulent material on aspiration, and subsequently responding to penicillin without further aspirations. On admission, temperature was 101.4 F, pulse, 90, respiration, 24, and blood pressure, 155/100. He was a normally developed, muscular male who was well oriented, but who exhibited peculiar ideation. He was lethargic, but easily arousable, and his gait was unsteady. There was diminished hearing bilaterally, expecially for higher tones. The remaining cranial nerves revealed no deficit. Chaddock, Oppenheim, and Babinski's signs were present on the right, and the left ankle jerk was diminished. Hemoglobin was 14.8 g/100 ml, hematocrit 44%, WBC 8,100, 77% neutrophils. Urine specific gravity was 1.021. Admission serum Na was 135; Cl, 88; K, 3.1 and bicarbonate, 29 mEq/L. Serum Ca, PO_4, GO transaminase, amylase, acid and alkaline phosphatase, albumin, globulin, cephalin flocculation, blood and spinal fluid serology, routine febrile and heterophil agglutinations were normal or negative. Cultures of sputum, urine, blood and cerebrospinal fluid were negative for ordinary pathogens, *M. tuberculosis,* and fungi. India ink preparations, and complexment fixation and hemagglutination tests on acute and chronic serum showed no abnormality. Skull films showed an upward shift of the pineal. Lumbar puncture revealed an opening pressure of 330 mm saline and a low glucose (25 mg/100 ml with concomitant blood glucose of 93 mg/100 ml). Spinal fluid protein was 142 mg/100 ml with 35 cells (8 neutrophils and 26 lymphocytes)/mm^8. Although acid-fast organisms were not seen on direct smear, isoniazid, streptomycin and p-aminosalicylic acid therapy was begun on the third hospital day. The patient was afebrile by the 11th day, but was increasingly lethargic and confused. At the same time serum sodium and potassium had fallen. It was found that fluid administration had to be limited to 1,000 ml/day. Urine osmolalities were 593 and 505 mOsm/kg at times when serum osmolality was 252 mOsm/kg. With fluid restriction of 1,000 ml/day the patient complained of no thirst, his sensorium cleared, and serum electrolyte values returned to normal. Audiogram prior to streptomycin therapy confirmed a bilateral auditory deficit and 6th and 7th nerve deficits were subsequently noted. Upward shift of the pineal on plain skull x-rays, together with cranial nerve involvement, were interpreted as brain stem arachnoiditis consistent with presumptive tuberculous meningitis. These findings showed marked remission between the

20th and 30th days. By the 55th hospital day the patient could tolerate daily fluid intakes of 3,000 ml without a reduction in serum sodium.

Case 4, W.M.W. This patient was a 43-year-old woman who noted midline low back pain without radiation three years before admission. Initially, the pain could be relieved by symptomatic measures, but more recently it had increased in severity, had begun to radiate into the left hip and inguinal area, and was now made worse by coughing and sneezing. She was admitted to the orthopedic service at MCV on March 6, 1963. On admission the temperature was 98.4 F, the pulse, 86 and respirations, 18 per minute. There was joint tenderness at L4-L5, associated with moderately severe paravertebral muscle spasm. Straight leg raising produced pain at 45°. No neurologic deficit was demonstrable. The pain was not noticeably benefited by continuous traction, and exploration for a herniated nucleus pulposus was carried out on the fifth hospital day. Post-operatively the patient had an elevated temperature, leucocytosis and a urine culture positive for *E. coli*. Despite treatment for urinary tract infection, daily temperature spikes continued as high as 102.6 F. She complained of weakness and numbness of both lower limbs, and showed objective weakness of the right foot and ankle and diminished sensation over both feet. Mental confusion, nuchal rigidity and divergent strabismus were noted two days later. Left patellar and both triceps reflexes were absent and the right patellar reflex was weak. The patient was lethargic and would reply only to direct questioning. Lumbar spinal fluid pressure was 410 mm saline with 102 cells/mm^3, predominantly lymphocytes. At the onset of confusion, serum Na was 117; Cl, 77; K, 2.8; bicarbonate, 22 mEq/L and BUN, 11 mg/100 ml. Ten days later serum Na was 112; K, 3.7 and BUN was less than 7 mg/100 ml. Urine osmolality was 450 mOsm/kg when serum osmolality was 250 mOsm/kg. Marked improvement in sensorium followed restriction of fluid intake to 1,000 ml/day, with rise in serum Na to 132 mEq/L. However, the peripheral neurologic deficit progressed to complete paraplegia. A myelogram done with simultaneous injection into the cisterna magna and into the lumbar space revealed a complete block from C7 to T4. Laminectomy revealed dense adhesive arachnoiditis. Microscopic appearance was compatible with tuberculous infection. Following a temperature elevation to 106 F, streptomycin, isoniazid and p-aminosalicylate therapy was administered with subsequent lysis of fever. Spinal fluid cultures and guinea pig innoculations were positive for *M. tuberculosis.*

Special Studies

Case 1. Water Loading and Alcohol Administration

A water load of 20 ml/kg water was given as 4% hexose solution intravenously. An indwelling catheter was used to collect urine, and blood samples were obtained three times by venipuncture. Cumulative volume of urine was recorded and replaced by additional intravenous fluid administration. After control urine collections at stable flow, 120 ml bourbon whiskey was given by mouth in eight minutes and urine collections were made at 12 to 25 minute intervals over a period of two hours.

Varying Sodium Intake

During a 37-day period, dietary sodium was 10 mM with periodic supplementation by oral sodium chloride tablets to increase the intake to 45 to 80 mM/day. On the indicated days, additional sodium was given in the form of hypertonic saline intravenously in the following amounts; 10th and 11th (410 mM); 21st, 22nd, 26th (425 mM). Water was restricted on the 13th to the 17th day; water intake was 1.0 to 2.4 L from the 18th to the 30th day; and was 0.3 to 0.8 L from the 31st to the 41st day. Thereafter water intake was from 0.5 to 2.5 L as regulated by the patient's desires. 9-α-fluorohydrocortisone was given on the 21st, and continued to the 41st day. Sodium chloride in tablet form was omitted; and the diet was changed to contain approximately 100 mM/day on the 38th day until the end of the study. On four occasions analyses of the diet revealed 85 to 104 mM sodium content. During the period of 9-α-fluorohydrocortisone administration, the patient received an additional 60 units of corticortropin on days 44 through 50.

Case 2. Sequential Water Loading-Salt Loading

These studies were carried out on February 7th and 27th, 1962 (138 days and 158 post-injury), on May 10th and 14th, 1962 (213 days and 220 days post-injury), and repeated one year later. Details of the test were as follows. Control weight, and blood and urine specimens for sodium content and total solute content, were obtained before water loading. The patient then ingested 20 ml water/kg over a one-hour period. We used an indwelling multiholed catheter to collect urine, and an inlying thin-walled 20 gauge needle with stylet to collect blood samples. Cumulative urine volume was recorded and replaced by additional ingested water. Inulin and sodium p-aminohippurate priming injections and sustaining infusions were begun, and after 30 minutes' equilibration time, urine was collected for clearance periods every 15 minutes, with midpoint blood collections. In the experiment where inulin space was measured, priming injection was omitted, and the infusion rate was accurately calibrated for use in the calculation. After 90 minutes (six clearance periods), infusion of 5% NaCl at the rate of 0.125 ml/kg/min was given over a period of 45 minutes. Clearance periods were continued for an additional 60 minutes after completion of this infusion.

Varying Sodium Intake

This was studied for a period of 24 days (days 118 through 142 post-injury) beginning with the patient's transfer to the medical service on January 16, 1962. He was placed upon a 10 mM/day sodium diet for eight days and was allowed to drink as much fluid as desired, which was 2 to 3 L/day. On the fifth day an additional 300 mM

sodium was given as 5% NaCl solution. On the ninth day dietary sodium was increased to 153 mM/day and an additional 500 mM sodium, as a 5% solution intravenously, was again administered. On day 15, fluid restriction to less than 1,000 ml a day was begun and sodium intake was lowered to 118 mM/day. These studies have been reported in more detail elsewhere (Haden and Knox, 1965).

Results

Case 1. Findings in a 43-day period of study are depicted in fig. 1. Serum sodium concentration fell from 121 to 110 mEq/L during sodium intake of 40 to 80 mEq/day, and water intake of 1.2 to 2.9 L/day in the initial nine days of the study. On days 9 and 10, the administration of a total of 1,120 mEq sodium caused a brief rise in serum sodium concentration from 108 to 120 mEq/L, but most of the administered sodium (913 mEq) appeared in the urine. The remainder was accountable by a slight increase in weight; and serum sodium promptly fell again to 106 mEq/L. An attempt to restitute serum sodium by water restriction alone was abandoned when serum sodium value fell to 99 mEq/L, although with maintenance of blood pressure at 140/80 mm Hg. A second large sodium load (980 mEq) was given as intravenous hypertonic saline and oral sodium chloride tablets on days 20 and 21, with a rise in serum sodium concentration to 122 mEq/L on day 22. On 80 mEq sodium/day plus 9-α-fluorohydrocortisone but without water restriction, serum sodium rose to 128 mEq/L but no higher; on the addition of water restriction it rose to 143 mEq/L on day 43. Thereafter it fluctuated between 128 and 140 mEq/L, the lower values being associated with water intake over 1.5 L/day.

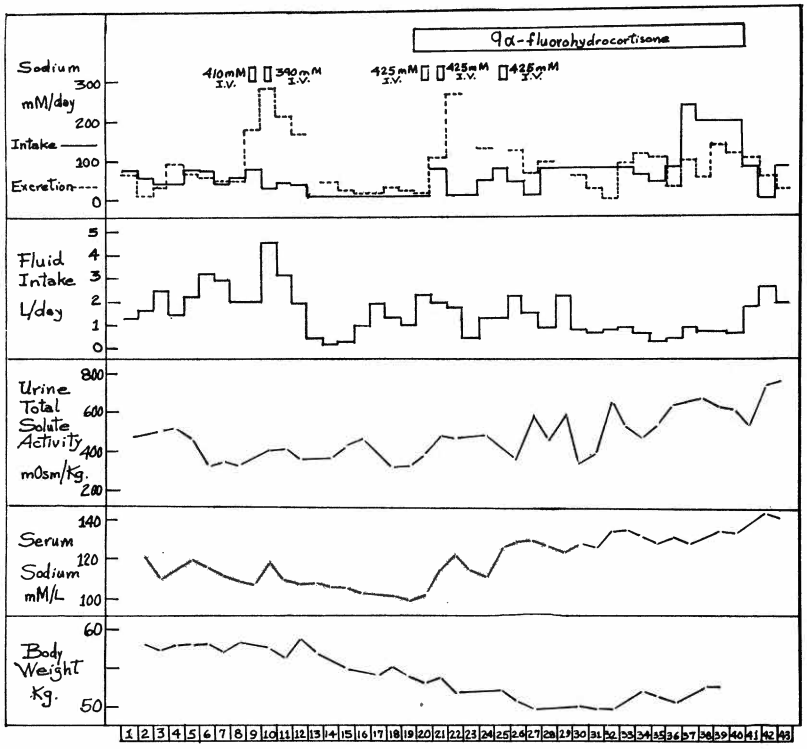

Fig. 1—Sodium balance, fluid intake, urine concentration, serum sodium and weight during 43-day period of study in Case 1.

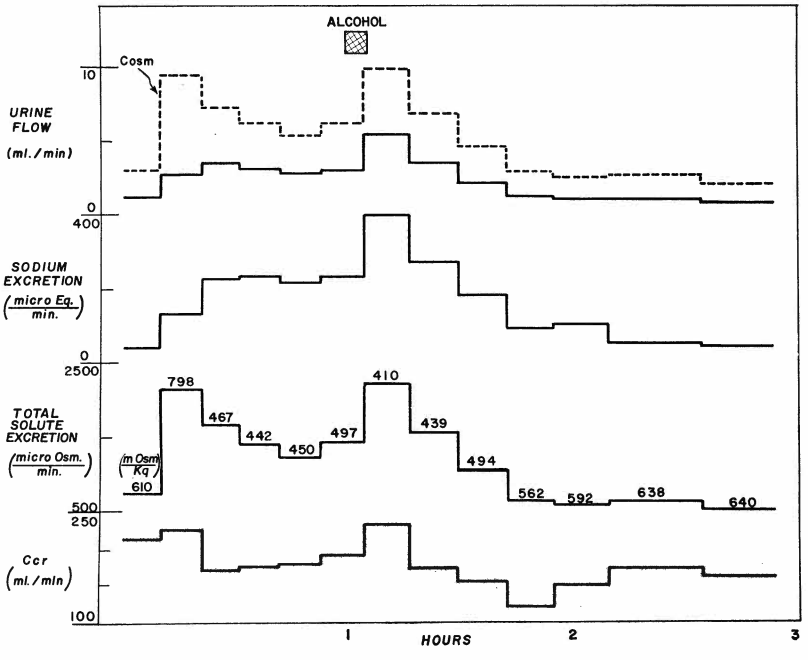

Fig. 2—Urine flow, sodium excretion, total solute excretion and creatinine clearance during water loading, before and after ethanol administration (48 g by mouth) in Case 1.

During this 43-day period and an additional 13 days of observation, urine total solute activity always exceeded that of serum by 70 mOsm/kg or more; minimal osmolal U/P ratio observed was 1.3. The range of urine osmolality was 288 to 866 mOsm/kg and 24-hour urine volume, 602 to 3,130 ml/day.

In an acute study (fig. 2) water loading failed to produce a dilute urine and revealed a maximal urine flow rate of 3.6 ml/min (minimal osmolality, 442 mOsm/kg). Urine flow rate increased to 5.4 ml/min during the first 10 minutes following alcohol ingestion but the urine remained hypertonic (minimal osmolality, 410 mOsm/kg). Serum sodium was 236 mOsm/kg, before and 224 mOsm/kg after; sodium excretion remained at 200 μEq/min throughout. Creatinine clearance, which was 202 ml/min/1.73m^2 (three periods) before water loading, fell to 173 ml/min/1.73m^2 (four periods) after alcohol ingestion. Inulin and PAH clearances were also measured when the patient was comparably hyponatremic (serum sodium 116 mEq/L, serum osmolality 236, mOsm/kg). Inulin clearance was 238 ml/min/1.73m^2, PAH clearance was 1,109 ml/min/1.73m^2, and filtration fraction was 0.30. The volume of distribution of inulin was 14.1 L (24% of body weight).

Case 2. During eight days on sodium restriction to 10 mEq/day, and ad libitum water ingestion (2,930 to 3,190 ml), minimal sodium excretion was 20 mEq/day and serum sodium fell to 107 mEq/L, rising only to 111 mEq/L with infusion of 300 mEq NaCl as 5% solution intravenously. Beginning with day nine, water intake was limited to less than 1,800 ml/day (870 to 1,800), and dietary sodium increased to 153 mEq/day, with rise in serum sodium to 125 mEq/L. Beginning with day 15, dietary sodium was decreased to 118 mEq/day and water limited to less than 1,000 ml/day (840 to 920) for three days, with rise of serum sodium to 138 mEq/L, following which water intake was again liberalized.

A sequential water loading and salt loading test (table 4) was done on the 22nd study day (four months post-injury) at which time serum sodium was 115 mEq/L and serum osmolality 242 mOsm/kg. Urine osmolality was 599 mOsm/kg water prior to water load, and urine sodium excretion rate 280 μEq/min (2.43% of filtered load). After the water load, serum sodium fell to 113 mEq/L, and serum osmolality to 295 mOsm/kg. Urine osmolality fell from 599 to 301 mOsm/kg following water load, and urine sodium excretion rate rose to 730 mEq/min (6.34% of filtered load). After completion of infusion of 425 mEq sodium as hypertonic NaCl, serum sodium was essentially unchanged at 115 mEq/L with a serum osmolality of 265 mOsm/kg. Urine osmolality fell slightly more to 281 mOsm/kg, with urine sodium excretion rate rising to 1,240 μEq/min (10.8% of filtered load). Net reabsorption of solute free water was present throughout (1.9 — 2.5 ml/min.) Inulin clearance was 116 ml/min/1.73m^2 (for his single kidney) and inulin space 16.0 L (26% of body weight).

This patient was restudied in May 1962, 10 weeks later (eight months post-injury). It was now noted from random specific gravities that he occasionally had dilute urine. After water loading, he had a free water clearance of only 0.48 ml/min, with a minimum urine osmolality of 233 mOsm/kg (serum osmolality being 264 initially, falling to 253). On salt loading, free water clearance doubled (to 1.09 ml/min), with no fall in minimum urine osmolality (the latter rose to 266 mOsm/kg). Minute sodium excretion rose from 468 μM/min initially to 614 at termination of the water load, and did not exceed 1.3% of filtered load. Inulin clearance was 69 ml/min/1.73m^2.

On the final study, one year later (May, 1963), serum sodium was 133 and serum osmolality 244. On water loading, serum sodium fell to 129, and serum osmolality to 240. Free water clearance was 1.5 ml/min and minimum urine osmolality, 200 mOsm/kg. On salt loading, free water clearance rose to 4.0 ml/min but minimum urine osmolality remained over 200 mOsm/kg. Urine sodium excretion rate rose from 214 to 1,644 μEq/min (from 1.5% to 11.8% of filtered load) and he again had a high inulin clearance (97ml/min/1.73m^2).

Discussion

These cases illustrate the typical findings in a naturally occurring

TABLE 1
A Classification of Hyponatremic Syndromes

Hyponatremic Syndrome	Low Filtration	High Filtration
I. (A) Edematous (Na^+ retaining)	Circulatory failure	Primary Na retention: 1) Cirrhosis 2) Nephrosis
(B) Non-edematous (Na^+ wasting)	Renal saline volume loss: 1) Mineralocorticoid failure 2) Renal failure simulating mineralocorticoid failure	Primary H_2O retention: 1) Inappropriate vasopressin excess 2) Glucocorticoid failure without mineralocorticoid failure
II. Non-edematous (Na^+ retaining)	Non-renal saline volume loss (appropriate vasopressin excess)	

syndrome simulating the effects of prolonged exogenous vasopressin administration in man (Leaf et al., 1953; Levinsky, Davidson, and Berliner, 1959; Stormant and Waterhouse, 1961; Jaenicke and Waterhouse, 1961), to which Schwartz and co-workers (1957) have given the designation "syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone." Since it is still not possible to measure serum ADH activity directly with ease and precision, the diagnosis of this entity remains a presumptive one. The criteria presently accepted as warranting its presumption are:

Diagnostic Features of the Syndrome

(1) Hyponatremia, either asymptomatic or associated with frank water intoxication, is the usual reason for suspecting the syndrome.

(2) Hypertonic urine is excreted in the presence of hypotonicity of body fluids. The latter may be confidently inferred from hyponatremia if this is unassociated with hyperglycemia or hyperlipemia. It is not actually necessary that the tonicity of urine exceed that of serum water, merely that it exceed that of the intake, if solute and water intake can be readily calculated. In practice, urine usually is markedly dilute (osmolal urine to serum water ratio as low as 1:5) in the absence of vasopressin, which would be the expected response to true body fluid hypotonicity.

(3) Renal sodium conservation, as evidenced by low urine sodium concentrations, does not occur in association with hyponatremia in these patients, nor do they develop edema. Edema is absent despite the fact that extracellular fluid space and total body water are expanded.

(4) Absence of azotemia, hypotension, or stigmata of so-called dehydration distinguish this syndrome from adrenocortical failure and from the salt-wasting forms of primary renal disease. Although the salt-wasting is to a certain extent reversible by mineralocorticoid hormone administration, this may be less efficient than water restriction alone.

(5) The response to hypertonic salt infusion is augmented urinary salt loss; hence this method of therapy is usually ineffectual in increasing serum sodium concentration.

Differential Diagnosis of Hyponatremic Syndromes

In table 1, the relation of this particular form of hyponatremia to other hyponatremic syndromes is considered. Usually the edematous hyponatremic syndromes may be identified by the presence of edema although recent therapy or sodium restriction may obscure the tendency. With or without edema these patients are distinguishable by their sodium retaining tendency, manifesting a) a low urine sodium excretion regardless of its sufficiency in the diet, and b) a tendency to reaccumulate edema if its intake is liberalized. In both of these respects such patients differ from the patient who has a genuine saline volume deficit due to losses by an extrarenal route, in the face of unimpaired and appropriately invoked renal mechanisms for conserving both sodium and water. The latter patient tends to maintain circulatory filling at the cost of some dilution of body fluids (appropriate vasopressin excess). Because of the importance of a low filtration rate in the genesis of cardiac edema, patients with hyponatremia may be classified, frequently on the basis of serum urea nitrogen concentration alone, into low and high filtration states. Edematous patients with cirrhosis and the nephrotic syndrome frequently have supernormal filtration rates and a serum urea nitrogen concentration that is either normal or distinctly low. In the non-edematous hyponatremic syndromes, serum urea nitrogen again is helpful in distinguishing low filtration states, such as Addison's disease or the salt-wasting forms of renal disease, from the entity under discussion, where filtration rate may be high and serum urea nitrogen low.

In table 1 the high filtration variety of non-edematous hyponatremia is referred to as "Primary Water Retention" in deference to

TABLE 2
Distinguishing Features of Three Varieties of Hyponatremia

	Hypoadrenal	Hypopituitary	Inappropriate ADH
I. Pathophysiology			
1) Defect	Mineralocorticoid and glucocorticoid deficiency	Glucocorticoid deficiency	Vasopressin excess
2) Extracellular fluid volume	↓	Normal	↑
II. Signs			
1) Urine Na^+	↓	↑	↑
2) Urea N	↑	May be low	May be low
3) Hypotension	+	0	0
III. Symptoms	+	0	+
IV. Response to R_x			
1) Saline	+	+	0
2) Cortisol	+	+	0
3) H_2O restriction	0	0	+

the fact that two possibly separable defects may account for the failure of urinary dilution inherent in such a syndrome. In the one circumstance, exemplified by the cases discussed here, a normal tubular mechanism for diluting the isotonic filtrate may be present, only to have its effect vitiated by the presence of vasopressin under circumstances normally effecting its suppression. In the other circumstance, there may be a fault in the diluting mechanism such that there is failure to dilute the urine appropriately, despite preservation of physiologic suppression of vasopressin, though perhaps at a "reset" level of plasma osmolality (Aubry et al., 1963). Van't Hoff and Zilva (1961), and Goldberg and Handler (1960) have called attention to this entity, occurring in hypopituitarism, with absence of the effects of glucocorticoids, though not of mineralocorticoids, upon the renal tubule. The work of Kleeman, Maxwell, and Rockney (1958) suggests that there is a permissive effect of cortisol upon water excretion, residing in its property of "inhibiting back diffusion or reabsorption of water in the loop of Henle, distal tubule, the concentrating segment," in the absence of vasopressin.

In table 2 the features of hyponatremia in Addison's disease (high urea N) are contrasted with those of hypopituitarism and of vasopressin excess (both characterized by a low urea N). The low urea N in hypopituitarism may in part connote less urea production, and hence may not infer a supernormal filtration rate to the same degree as would an equally low urea N in vasopressin excess. The distinction between the latter two entities, rather than simply lumping them as "Primary Water Retention," is of some importance in that treatment with cortisol is efficacious in hypopituitarism. Furthermore, other associated and correctible factors, such as pituitary myxedema may contribute to water retention, probably in some instances by a mechanism of vasopress in excess (Goldberg and Reivich, 1962; Holvey et al., 1964; Oettinger, Talner, and Ferris, 1965).

TABLE 3
Etiologic Categories Associated With "Cerebral Hyponatremia"

Etiology	References
Encephalitis, etiology unknown	Peters et al., 1950
herpes simplex	Rovit and Sigler, 1964
Cerebral hemorrhage	Peters et al., 1950
	Goldberg and Handler, 1960
Bulbar poliomyelitis	Peters et al., 1950
Cerebral thrombosis	Peters et al., 1950
	Goldberg and Reivich, 1962
	Holvey et al., 1964
	Ottinger et al., 1965
	Goldberg and Handler, 1960
Brain tumor	Peters et al., 1950
	Welt et al., 1952
	Goldberg and Handler, 1960
Head injury	Cort, 1954
	Carter et al., 1959; 1961
	Vogel, 1963
	Haden, 1965
Meningitis, tuberculous	Rapoport et al., 1951
	Harrison et al., 1952
	Cheek, 1956
	Arblaster, 1957
Ascending paralysis	Fourman and Lesson, 1958
Paroxysmal cerebral dysfunction	Epstein and Levitin, 1959
	Epstein et al., 1961
Congenital cerebral malformation	McCrory and Macauley, 1957
Idiopathic	Grumer et al., 1962
Porphyria	Ludwig and Goldberg, 1962; 1963
	Hellman et al., 1962
	Recant and Lacy, 1963

Possible Mechanisms of Inappropriate Antidiuresis

Inappropriate antidiuresis has been reported in a variety of clinical circumstances. If it is clear that identifiable non-osmotic stimuli to vasopressin (Wesson, 1965) such as pain, excitement, circulatory stress or pharmacologic agents (ether, cyclopropane, nitrous oxide, barbiturates, morphine, nicotine, catecholamines) are no longer operative, the alternatives of autonomy of vasopressin secretion of either pituitary or extrapituitary origin must be considered. Where the cause appears to be ungoverned drive to the supraoptico-hypophyseal tract, it has been postulated that there may be either stimulation through aberrent reflexes, or lack of inhibition as a consequence of interrupted neural pathways (Schwartz et al., 1957; Dossetor et al., 1961; Amatruda et al., 1963; Thorn and Transbøl, 1963). In patients with carcinoma of the lung, as in Case 1, it has been proposed that the liberation of a humoral substance from the tumor itself (Roberts, 1959; Dossetor et al., 1961) might account for sustained hypertonicity of the urine. Thus, reports of the presence in such patients of a antidiuretic substance in urine (Thorn and Transbøl, 1963) and antidiuretic material extracted from specimens of tumor are of considerable interest (Amatruda et al., 1963; Bower and Mason, 1964). In two of these reports (Amatruda et al., 1963; Thorn and Transbøl, 1963), employing incubation with thioglycollate, the antidiuretic material was indistinguishable from arginine vasopressin.

Carcinoma of the Lung

Previous reports indicate that carcinoma of the lung, particularly the oat cell type, which constitutes

the majority of tumors associated with inappropriate antidiuresis, may produce other biologically active materials with manifestations of adrenal cortical hyperfunction (Huth, 1961) and hypercalcemia (Lee, Jones, and Barreclough, 1964). These observations seem to lend credence to the possibility that many malignant lung tumors associated with inappropriate antidiuresis may themselves produce an antidiuretic hormone.

In Case 1 the lack of dilution following a water load and the administration of ethyl alcohol, a known inhibitor of vasopressin release, suggests that the mechanism for release of antidiuretic substance was not responsive to these suppressive stimuli and that the source of the hormone maintained a degree of autonomy. Similarly, other instances in which alcohol was administered under comparable circumstances in patients with carcinoma of the lung (Amatruda et al., 1963; Thorn and Transbøl, 1963; Bower and Mason, 1964), central nervous system disease (Epstein et al., 1961; Goldberg and Handler, 1960), and intermittent porphyria (Hellman, Tschudy, and Bartter, 1962) failed to result in a dilute urine. A patient with carcinoma of the lung (Thorn and Transbøl, 1963) and another with hypothyroidism (Goldberg and Reivich, 1962) demonstrated transient dilution of the urine with alcohol, although dilution was submaximal, indicating a defective mechanism for suppression of vasopressin.

The sustained production of a physiologic excess of antidiuretic substance by tumors of the lung is indicated by the absence of further concentration of the urine with administration of exogenous vasopressin (Amatruda et al., 1963; Bower and Mason, 1964). This is further suggested in a less direct manner by the observation in Cases 1 and 2 that over a long period of time there was a highly significant direct linear correlation ($p. < .001$) between the total solute concentration of the 24-hour urine collections and the daily serum sodium, irrespective of other considerations known to influence concentrating ability. Such a relationship has been described with prolonged administration of vasopressin and water (Jaenicke and Waterhouse, 1961) and the same tendency was noted in a patient with carcinoma of the lung (Schwartz et al., 1957). Thus, with continuous secretion of antidiuretic substance in maximal amounts, this correlation of serum sodium over a wide range with urine solute concentrations could, according to current concepts of the concentrating mechanism (Gottschalk, 1964), reflect primarily the state of tissue hydration, specifically that of the renal medulla.

"Cerebral" Hyponatremia

Case 2 is representative of the occurrence of hyponatremia in a wide variety of disorders affecting the central nervous system (Peters et al., 1950; Sims et al., 1950; Rapoport et al., 1951; Harrison et al., 1952; Welt et al., 1952; Cort, 1954; Cheek, 1956; Arblaster and Whitehead, 1957). More recently reported cases (McCrory and Macauley, 1957; Fourman and Lesson, 1958; Carter et al., 1959, 1961;

TABLE 4
Sequential Water Loading–Saline Loading Tests in Case 2

Date	Plasma Osmolality	Urine Osmolality	Urine to Plasma Concentration Rate	Urine Flow Ratio	Urine-Sodium Concentration	Urine-Sodium Excretion Rate	Free Water Clearance	Comment
	mOsm/L	mOsm/L	ml/min		mM/L	mM/min	ml/min	
2/7/62	242	599	2.48	1.6	175	280	-2.37	Baseline
	235	301	1.28	7.8	107	203	-1.90	Water Load
	245	320	1.31	12.4	131	1624	-2.80	Saline Load
2/27/62	260	729	2.80	0.7	152	106	-1.26	Baseline
	250	539	2.16	2.2	156	343	-2.55	Water Load
	288	514	1.78	2.0	218	436	-1.98	Saline Load
5/14/62	264	480	1.82	1.6	108	173	-1.32	Baseline
	252	243	0.96	6.4	84	538	+0.48	Water Load
	234	275	1.18	7.3	99	723	+1.09	Saline Load
5/7/63	244	510	2.09	1.6	110	176	-1.70	Baseline
	256	200	0.78	10.0	84	840	+1.20	Water Load
	280	236	0.84	24.4	99	2416	+4.10	Saline Load

Epstein and Levitin, 1959, 1961; Goldberg and Handler, 1960; Goldberg and Reivich, 1962; Grumer et al., 1962; Vogel, 1963; Holvey et al., 1964; Haden and Knox, 1965 Oettinger et al., 1965; Wesson, 1965) in which the authors have emphasized the primacy of inappropriate antidiuresis and a resemblance to the syndrome described by Schwartz et al. (1957) are included in table 3. Of particular interest is a case of hyponatremia following head injury reported by Carter et al. (1961). Because of the similarity of this case to Case 2 of the present report, studies patterned on those carried out by Carter et al. were performed in this patient. The normal response to an acute water load (20 ml/kg) is dilution of plasma water by some 20 mOsm/kg, (e.g., from 270 to 250), and a lowering of urine osmolality to less than 100 mOsm/kg. Failure of the expected urinary response could mean absence of an adequate stimulus (in the form of a decrease in plasma osmolality) to suppress vasopressin secretion. It could also mean that the stimulus threshold has been "reset" to a lower level, say 240 mOsm/kg, so that the degree of hypotonicity attained is no longer an appropriate stimulus. The response to hypertonic saline may help separate a hypothetical osmotic reset from autonomous or continuous vasopressin excess as classically seen in the syndrome described by Schwartz et al. (1957). In osmotic reset, the rise in plasma osmolality attendant upon hypertonic saline infusion, is usually accompanied by a further rise in urine osmolality from an isotonic level and a reciprocal decrease in urine flow. In the presence of continuous vasopressin activity, virtually no effect is seen except that in some instances there is a slight further rise in urine osmolality from an already hypertonic level. The rise is proportionate to the increase effected in plasma osmolality, so that the "U/P ratio" is not increased. This was the response seen initially in the patient of Carter et al. and in our Case 2. However, after some months, it became apparent that the patient could, sporadically, though by no means appropriately, produce a dilute urine, with a continued, though less severe, tendency to plasma hypotonicity, if excess fluid intake was not scrupulously avoided. As in the patient of Carter et al. we found that the patient could now (table 4) partially suppress vasopressin activity under the stimulus of plasma volume expansion (following hypertonic saline infusion), producing a urine slightly hypotonic to plasma. The patient still did not, however, dilute his urine normally in response to dilution (following water loading).

Summary

We have reviewed some of the features of hyponatremic syndromes, unassociated with sodium retention and edema, but associated with primary water retention. The syndromes were probably caused by excessive vasopressin activity, in the presence of normal circulatory, renal and adreno-cortical function. Underlying diseases, including bronchogenic carcinoma, head injury, and tuberculous meningitis, illustrated the diverse etiologic bases of this condition.

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