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Duck or Rabbit? Cerebral Salt Wasting and SIADH in Acute Brain Injury

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The psychologist Joseph Jastrow was fascinated with optic illusions. He introduced several of them in his 1901 book *Facts and Fable in Psychology*. He also introduced to the US audience, the now well-known ambiguous image that can be seen in two ways—as either a duck or as a rabbit.

The history of salt wasting and acute brain injury may be a good example of this type of perception. It depends on how you look at it. Cerebral salt wasting and the syndrome of inappropriate antidiuretic hormone (SIADH) share several serum and urinary laboratory criteria. But diagnosing one or the other leads to completely different treatments (fluid restriction versus sodium supplementation and volume expansion), and either treatment has major clinical downstream repercussions. Herein, I present a history of medical ideas and historical interpretations of enhanced diuresis and hyponatremia in acute brain injury, such as aneurysmal subarachnoid hemorrhage or central nervous system infections. Peters and associates are credited with one of the first detailed descriptions of salt wasting after a brain injury [1], but Cort [2] named the syndrome "cerebral salt wasting" when also reporting on a markedly dehydrated patient with a thalamic tumor. This indicated a further connection between the hypothalamus and proximal tubule of the kidney involved with sodium reabsorption.

Previous Observations

The experiments of Jungmann and Meyer in 1913 demonstrated that lesions in the medulla and anterior hypothalamus produced polyuria and increased sodium excretion in the urine (hypothalamic polydipsia) [3]. This was different from diabetes insipidus, which was predominantly aquaresis. During these early years, serum sodium could not be measured, but the key finding of hyponatremia in these acute neurologic disorders became better recognized after the flame photometer became widely available.

Observations of hyponatremia in several brain disorders came out of Yale University Medical Center, first by John P. Peters in 1950 [1] (Fig. 1) and later by J. H. Cort in 1952 [2]. Clinicians during this period reported most often on hyponatremia in patients with tuberculous meningitis. Peters and associates described three patients with acute encephalitis of undetermined etiology—presumably stroke (coma after acute headache and hypertensive emergency)—and bulbar poliomyelitis with severe hyponatremia in whom balance studies revealed excessive sodium loss in the urine during severe hyponatremia. Hyponatremia could not be corrected by high salt intake ("During the latter part of his hospital course, his intake of salt was that contained in the usual ward diet with free access to a salt-shaker [1]") or mineralocorticoid administration, and urinary secretion of sodium remained high. Adrenal and pituitary function tests were normal. Clinically, these patients became dehydrated despite fluid intake of several liters in the previous day. With volume expansion, urinary sodium loss increased (Fig. 2). After recovery from encephalitis, salt wasting subsided or diminished.

Two explanations were offered. The first explanation was excitation of the pituitary gland modified by the central nervous system. Such a lesion may "disorganize an automatic sequence that normally leads to the secretion of ACTH and in turn of salt retaining hormone from the adrenal cortex [1]." Peters and associates also speculated about a direct nervous influence of the central nervous system on the kidney, which, in turn, could modify the tubular salt reabsorption. Abnormality in the nerves supplied to the kidneys could lead to this change in renal hemodynamics.

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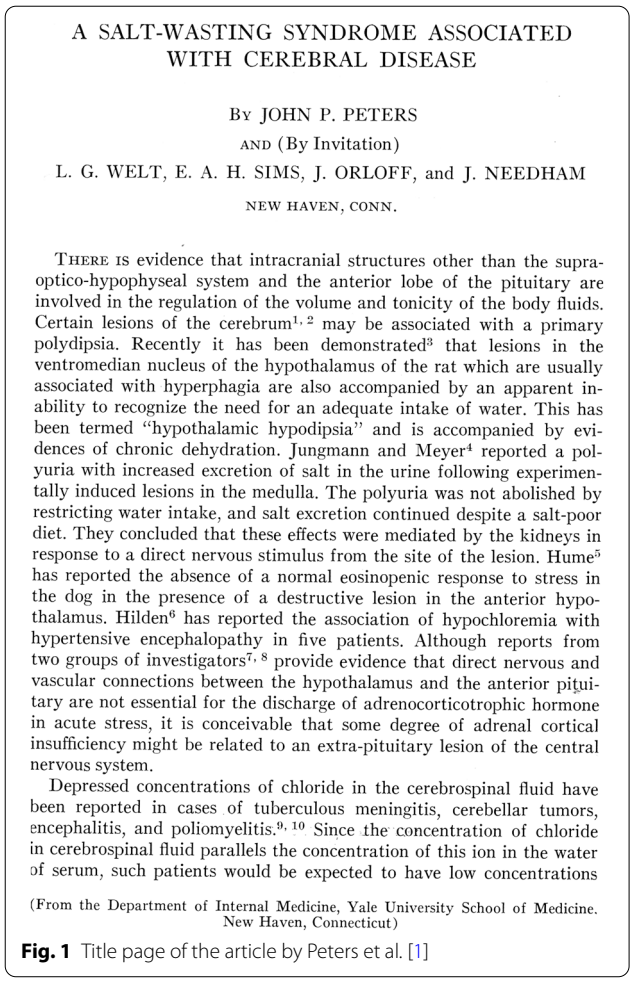

A SALT-WASTING SYNDROME ASSOCIATED WITH CEREBRAL DISEASE

By JOHN P. PETERS
and (By Invitation)
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THERE IS evidence that intracranial structures other than the supra-optico-hypophyseal system and the anterior lobe of the pituitary are involved in the regulation of the volume and tonicity of the body fluids. Certain lesions of the cerebrum[1, 2] may be associated with a primary polydipsia. Recently it has been demonstrated[3] that lesions in the ventromedian nucleus of the hypothalamus of the rat which are usually associated with hyperphagia are also accompanied by an apparent inability to recognize the need for an adequate intake of water. This has been termed "hypothalamic hypodipsia" and is accompanied by evidences of chronic dehydration. Jungmann and Meyer[4] reported a polyuria with increased excretion of salt in the urine following experimentally induced lesions in the medulla. The polyuria was not abolished by restricting water intake, and salt excretion continued despite a salt-poor diet. They concluded that these effects were mediated by the kidneys in response to a direct nervous stimulus from the site of the lesion. Hume[5] has reported the absence of a normal eosinopenic response to stress in the dog in the presence of a destructive lesion in the anterior hypothalamus. Hilden[6] has reported the association of hypochloremia with hypertensive encephalopathy in five patients. Although reports from two groups of investigators[7, 8] provide evidence that direct nervous and vascular connections between the hypothalamus and the anterior pituitary are not essential for the discharge of adrenocorticotrophic hormone in acute stress, it is conceivable that some degree of adrenal cortical insufficiency might be related to an extra-pituitary lesion of the central nervous system.

Depressed concentrations of chloride in the cerebrospinal fluid have been reported in cases of tuberculous meningitis, cerebellar tumors, encephalitis, and poliomyelitis.[9, 10] Since the concentration of chloride in cerebrospinal fluid parallels the concentration of this ion in the water of serum, such patients would be expected to have low concentrations

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Fig. 1 Title page of the article by Peters et al. [1]

Why salt wasting existed in acute brain lesions was further elaborated in the discussion section of the article, with one of the contributors suggesting that cerebral salt wasting was a compensatory mechanism of the brain to reduce brain swelling. But the patient's level of consciousness improved after correction and this improvement would not be expected if the hyponatremia was a compensatory mechanism. Peters [1] responded to this explanation as follows:

> *I tried to bring out the point that this reduction of serum electrolytes is not a reaction that can be neglected, but that it has very serious implications that are manifested not only in systemic symptoms, but also in cerebral symptoms. In the first patient, for example, when we raised his sodium to normal and restored his electrolytes, he became alert for the first time, and the mental improvement after that was striking. I do not believe, therefore, that this is a protective mechanism, because reversing it benefits the cerebrum.*

In the three cases cited, the sodium levels declined to 124 mEq/L, 118 mEq/L, and 117 mEq/L. All patients responded to increased salt intake with increased plasma sodium levels. Eventually, the discussants decided that the most probable explanation for urinary sodium loss was decreased proximal tubular reabsorption of sodium. Treatment was discussed and focused on increasing salt intake.

Bizarrely enough, the some insight came from a study of neck compression on sodium excretion in patients in cardiac failure. A blood pressure cuff was wrapped around the study participant's neck and sustained at a pressure of 20 mm Hg. Neck compression under conditions that cause significant increments in sodium excretion of normal study participants failed to increase sodium excretion in four patients with congestive heart failure [4].

A Paradigm Shift

In 1967, Frederic Bartter and William B. Schwartz [5] introduced and described SIADH, which promptly replaced the term "cerebral salt wasting syndrome" (CSW). They described how continuous secretions of antidiuretic hormone (ADH)—not appropriate to changes in plasma osmolality—would result in expansion of vascular volume and dilutional hyponatremia. Soon, other central nervous system disorders associated with hyponatremia, including herpes simplex encephalitis, tuberculous meningitis, brain abscess, cerebral infarction, and brain tumors, were automatically diagnosed as SIADH. Glomerular filtration rate and aldosterone were the first two identified controllers of renal sodium excretion. A third factor was discovered when H. E. de Wardener and colleagues [6] showed that volume expansion natriuresis still occurred in dogs given supramaximal doses of mineralocorticoids, but an increase in the glomerular filtration rate did not occur. Follow-up studies documented increased natriuretic peptides, endogenous digitalis-like factor and ouabain-like compounds, negative sodium balance, and reduced central venous pressure.

However, it soon became obvious that SIADH was often diagnosed without a valid basis. The first suggestion to reconsider CSW started with a key article in the *Journal of Neurosurgery* in 1981 [7]. This study found contracted blood volumes (using isotope studies) in hyponatremia after aneurysmal subarachnoid hemorrhage.

The term "cerebral salt wasting syndrome" resurfaced, and over the years, hyponatremia after central nervous system disease became CSW, then SIADH, and then CSW again. The clinical and laboratory features are nearly identical. Studies documented intravascular

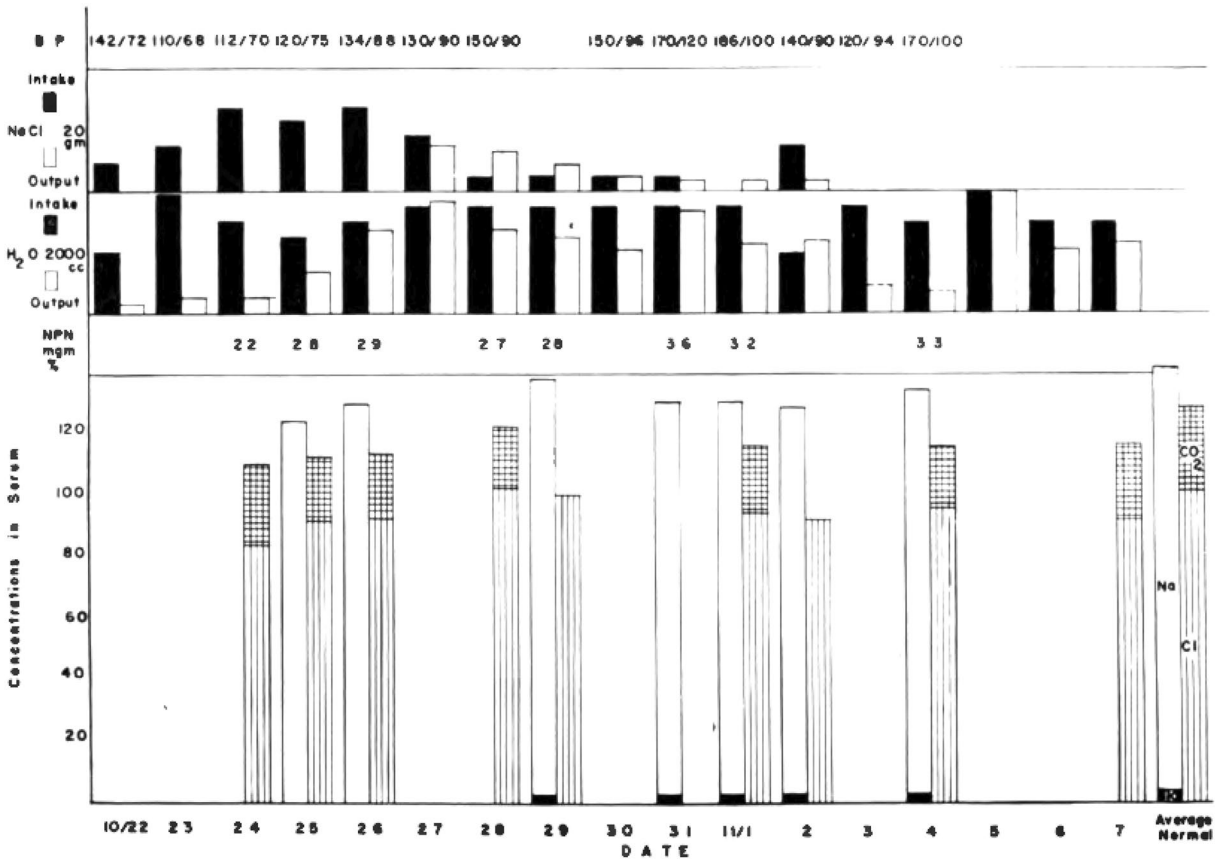

Fig. 2 Sodium balances in case III. "On November 1 she received no salt. Despite the depressed concentration of sodium in the serum the negative salt balance continued and the concentration of sodium in the serum fell still further to 125.6 mEq. per liter"

volume depletion with radioisotope dilution techniques, but these are not optimal methods. Opponents have argued that there is insufficient evidence of hypovolemia with ongoing natriuresis despite supporting studies. ADH studies are not helpful in CSW; decreased vascular volume resulting from high natriuresis and negative sodium balance actually triggers (appropriate) ADH secretion.

One theory is that CSW is a renal salt wasting syndrome, and salt replacement, mineralocorticoids, and corticosteroids restore the sodium balance. Some animal studies of subarachnoid hemorrhage (SAH) in rats cast doubt on the putative causative role of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in CSW [8]. Another challenge came from Ireland; in a recent study, 49 of 100 patients with SAH developed hyponatremia. The cause was SIADH in nearly 75% of cases, with some due to acute glucocorticoid insufficiency, but there were no cases of CSW [9]. Surprisingly, none of these patients had negative fluid balances. This was in contrast to the investigators' previous study with a well-documented single patient in whom they demonstrated a marked rise in both plasma ANP and plasma BNP concentrations in the early phase after SAH, with subsequent development of profound natriuresis, diuresis, blood volume contraction, and hypovolemic hyponatremia [10]. More recent studies showed strong support for CSW in traumatic brain injury using sodium balance and urinary biochemical analysis [11].

Over the years, there has been a practice reversal. Treatment currently involves trying to maintain a normovolemic state [12, 13], knowing that a relatively reduced cerebral blood flow from diuresis-induced hypovolemia could additionally harm the brain in susceptible patients. My colleagues and I began testing fludrocortisone in 1988, after we consulted a nephrologist (Van Brummelen) with an interest in sodium regulation. Van Brummelen suggested fludrocortisone acetate as a candidate because its mineralocorticoid activity enhances distal tubular sodium reabsorption in the kidney. Subsequent studies confirmed that this approach made physiological sense [14, 15].

In cerebral salt wasting, we often find a negative fluid balance. Rethinking the history of the diagnosis of hyponatremia in acute brain injury, we are left with a patient needing salt infusions and avoiding free water, but we must also prevent a negative fluid balance. The practice of strict fluid restriction has been discontinued.

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