Medicine Grand Rounds
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THE SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

The syndrome of inappropriate secretion of antidiuretic hormone, SIADH, may be defined as any pathophysiological state in which the secretory rate of ADH is greater than can be attributed to the stimuli which normally control the release of vasopressin. Implicit in this definition is that in the SIADH there exists either a nonpituitary source of antidiuretic hormone, ADH, or that the pituitary gland has become autonomous.

Clinical Findings and Symptoms of SIADH

The characteristic clinical features of the syndrome of inappropriate secretion of antidiuretic hormone result from unusually high rates of water retention at a time when serum osmolality is low. The salient findings of the SIADH are (1): 1) decreased serum sodium concentration (with associated decreased serum osmolality); 2) inappropriately high urinary excretion of sodium when the pateint is allowed free access to salt and water; and 3) urine osmolality which is higher than the plasma osmolality. However, there are many clinical states which may effect the aforementioned findings and thus these features are only of differential significance providing: 1) the patient has normal renal and adrenal function; 2) the patient is not on diuretics; and 3) there is no evidence of effective circulatory volume contraction.

Typically the SIADH has no specific clinical symptoms. If, however, patients do present with severe hyponatremia then the presenting complaints are secondary to water intoxication. The symptoms of water intoxication generally do not occur until the serum sodium concentration has dropped to less than 115 mEq/L. These symptoms are variable, but usually begin with irritability and confusion and may progress in severity to generalized convulsions and coma. Even death is not unusual at serum sodium concentrations of less than 90 mEq/L. The severity of water intoxication symptoms at a given serum sodium concentration is largely dependent on the rate at which hyponatremia was induced. The more rapid the fall in the serum sodium concentration, the more severe are the expected symptoms.

Renal Consequences of Increased Serum Concentration of ADH:

It has been shown that administration of exogenous ADH to laboratory animals results in: increased fractional excretion of phosphate from the proximal tubule (2); increased urinary excretion of sodium (3-5); however, it is now generally accepted that the major effect of ADH is to increase the back diffusion of free water from the collecting duct to the medullary interstitium. These events are depicted in Figure 1. It is

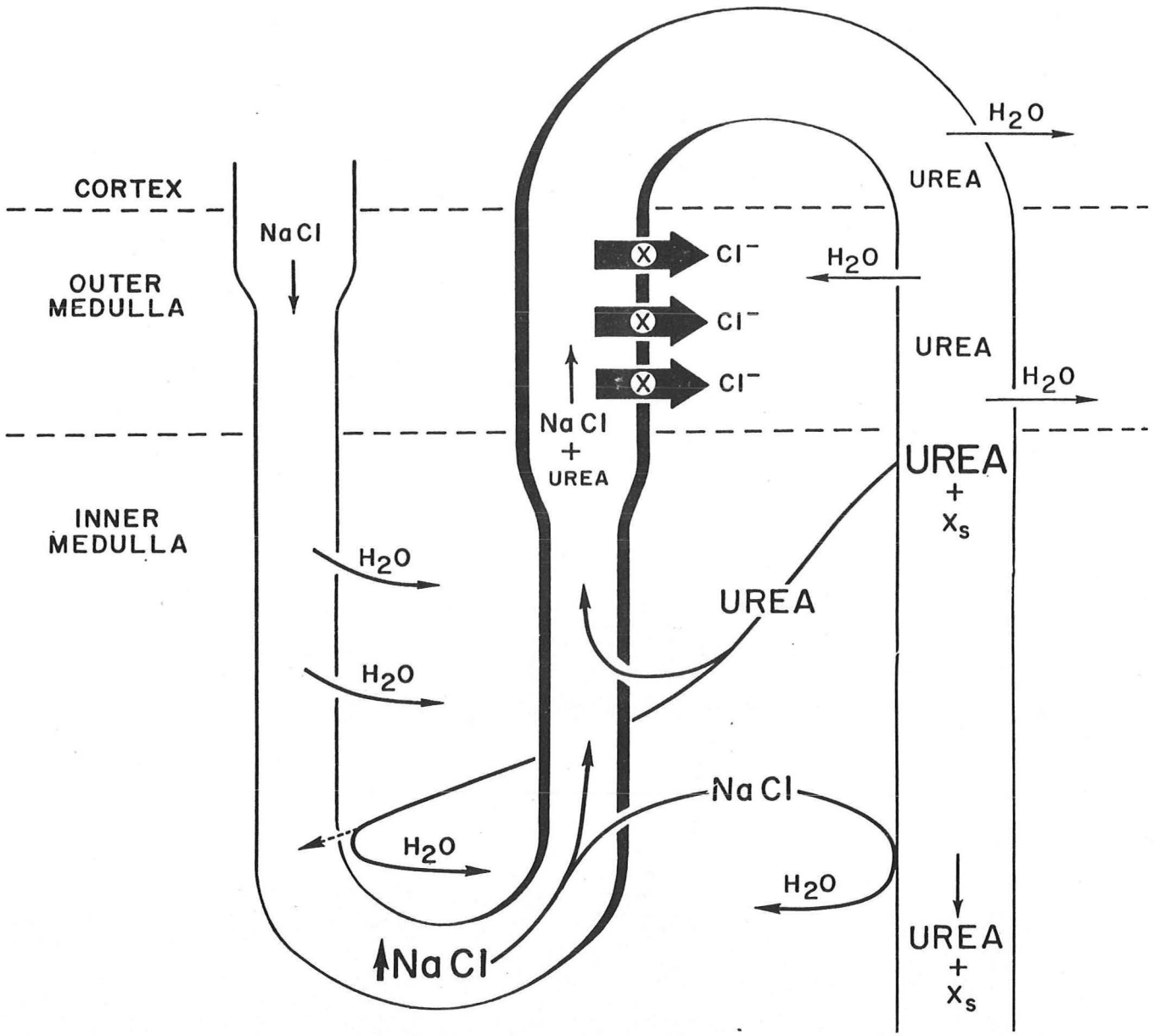

Figure 1: Schematics of the passive equilibration model of countercurrent multiplication system. Figure is modified from references 6 and 7. In the context of SIADH it is meant to illustrate that osmotic equilibration occurs in the collecting duct as a consequence of water abstraction. It is this back diffusion of "free water" which partly contributes to the development of hyponatremia.

this back diffusion of water which allows for osmotic equilibration between the collecting duct fluid and the medullary interstitium and thus results in the generation of urine which is more concentrated than plasma. The opposite would be true in the absence of ADH. Under the latter circumstances urine osmolality would be low and would reflect the activity of the chloride pump (8,9) and thus the diluting capacity of the thick ascending limb of Henle.

Regulation of ADH Secretory Rates:

Diverse physiological stimuli from the internal (and occasionally external) environment can elicit the release of ADH from the neurohypophysis. These can be grouped into three general areas: 1) blood volume; 2) serum osmolality; and 3) baroreceptor mediated stimuli.

Although a great number of previous investigations have attempted, by bioassay techniques, to assess the relative importance of volume and osmolar stimuli for release of vasopressin (10-17), it has not been until the recent development of a sensitive and specific radioimmunoassay for urine or plasma ADH (18-22) that this issue could be examined more precisely (22).

Figure 2, obtained from recent works of Dunn et al. (22), shows the response of plasma vasopressin concentration to progressive dehydration by water deprivation in a rat. As can be seen, there is a rapid increase in plasma ADH concentration which is evident within 12 hours. However, this experiment does not help to differentiate between the relative role of serum osmolality from blood volume since both the serum osmolality is increasing (top panel) and the blood volume is contracting as indicated by a rise in the hematocrit (middle panel).

Dunn and co-workers (22) have increased the serum osmolality without significant changes in blood volume by intraperitoneal injection of hypertonic saline. The results of these experiments are depicted in Figure 3 and show that within 15 minutes there is an approximate ten-fold increase in plasma ADH level associated with a six percent rise in plasma osmolality. In fact, in a great number of studies they found that an increase in plasma osmolality of only 1% resulted in a rise in plasma ADH level by 2.4 pg/ml (22).

These same workers have utilized the sensitive radioimmunoassay to examine the volume control of ADH secretory rates (22). These studies were performed by intraperitoneal injection of polyethylene glycol solutions containing varying amounts of NaCl. This procedure in their hands led to a rapid fall in plasma volume without significant effect on plasma

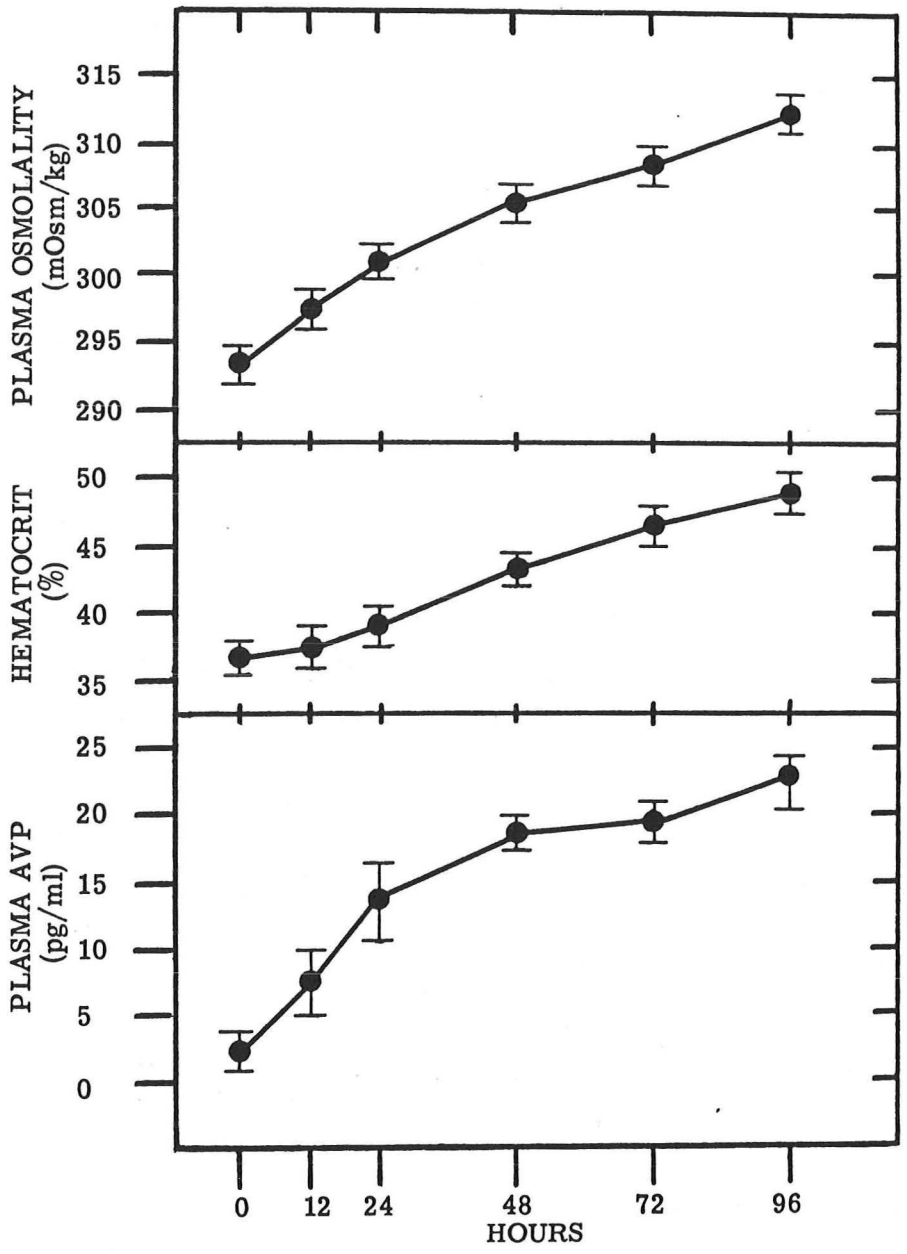

Figure 2: The effect of fluid deprivation on plasma osmolality, hematocrit and plasma ADH in rats (22).

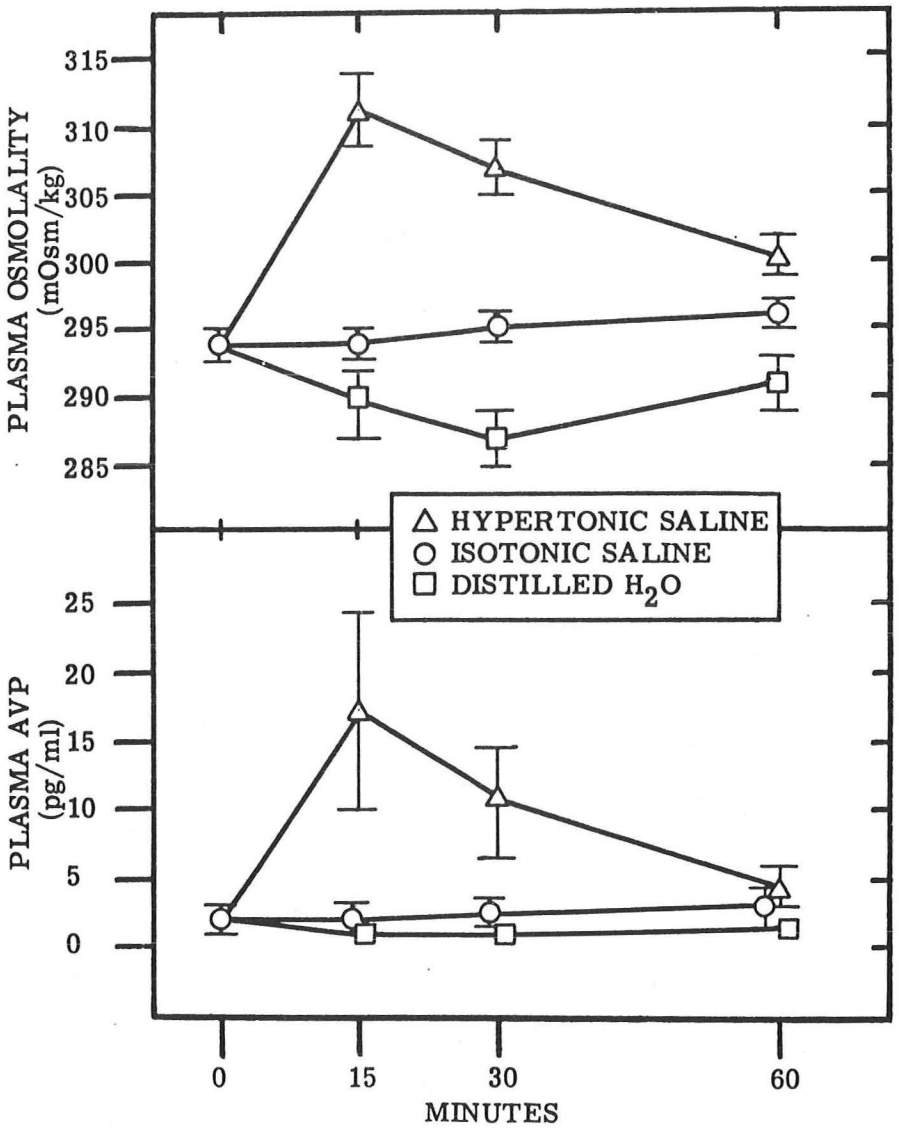

Figure 3: The effect of intraperitoneal injection (2 ml/100 gm body weight) of distilled water, isotonic or hypertonic saline on plasma osmolality (top panel) and plasma ADH (bottom panel) (22).

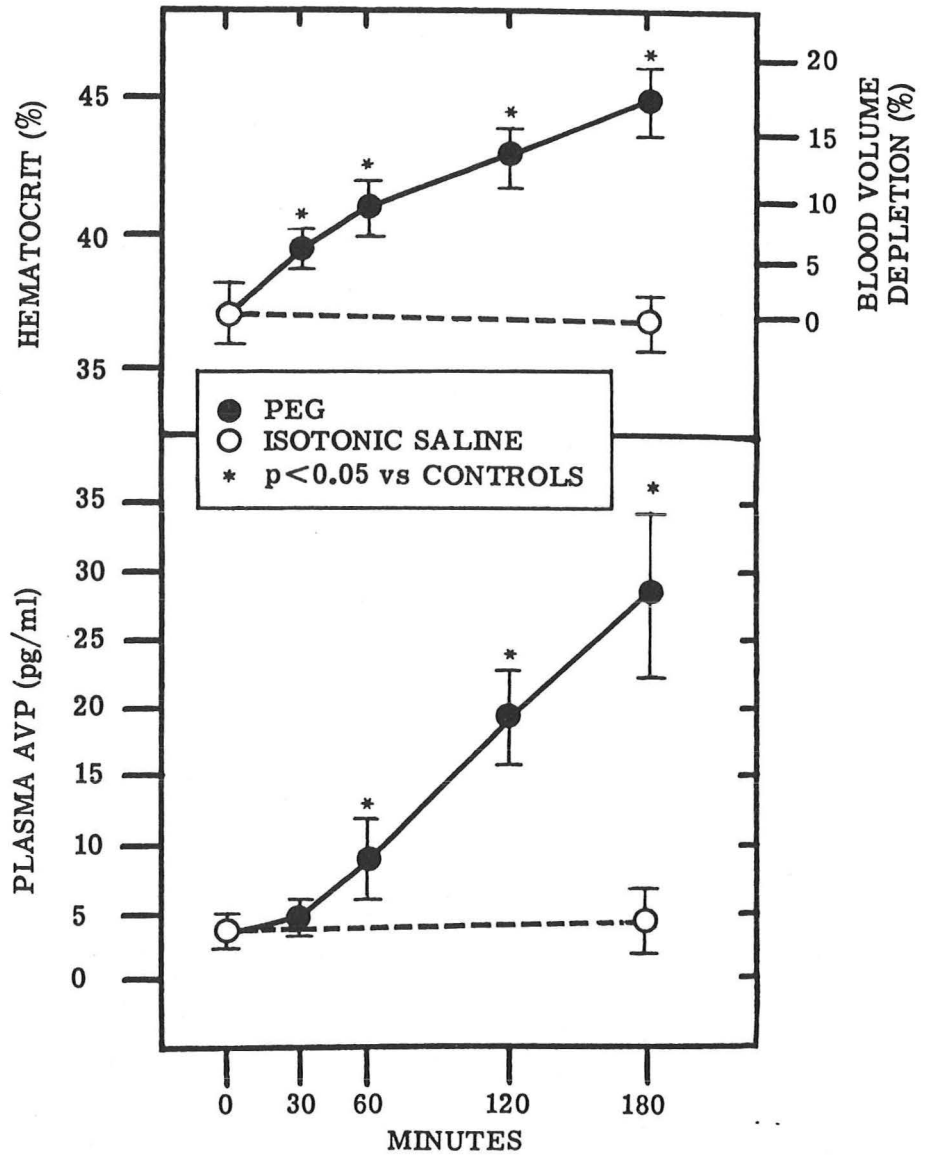

Figure 4: The effect of intraperitoneal injections of polyethylene glycol on blood volume and plasma ADH (22).

osmolality. The results are shown in Figure 4 and reveal that a rise in plasma ADH occurs with a progressive rise in the hematocrit. However, in contrast to the significant increase in ADH levels with 1% increase in serum osmolality, there was no change in plasma ADH until volume reductions

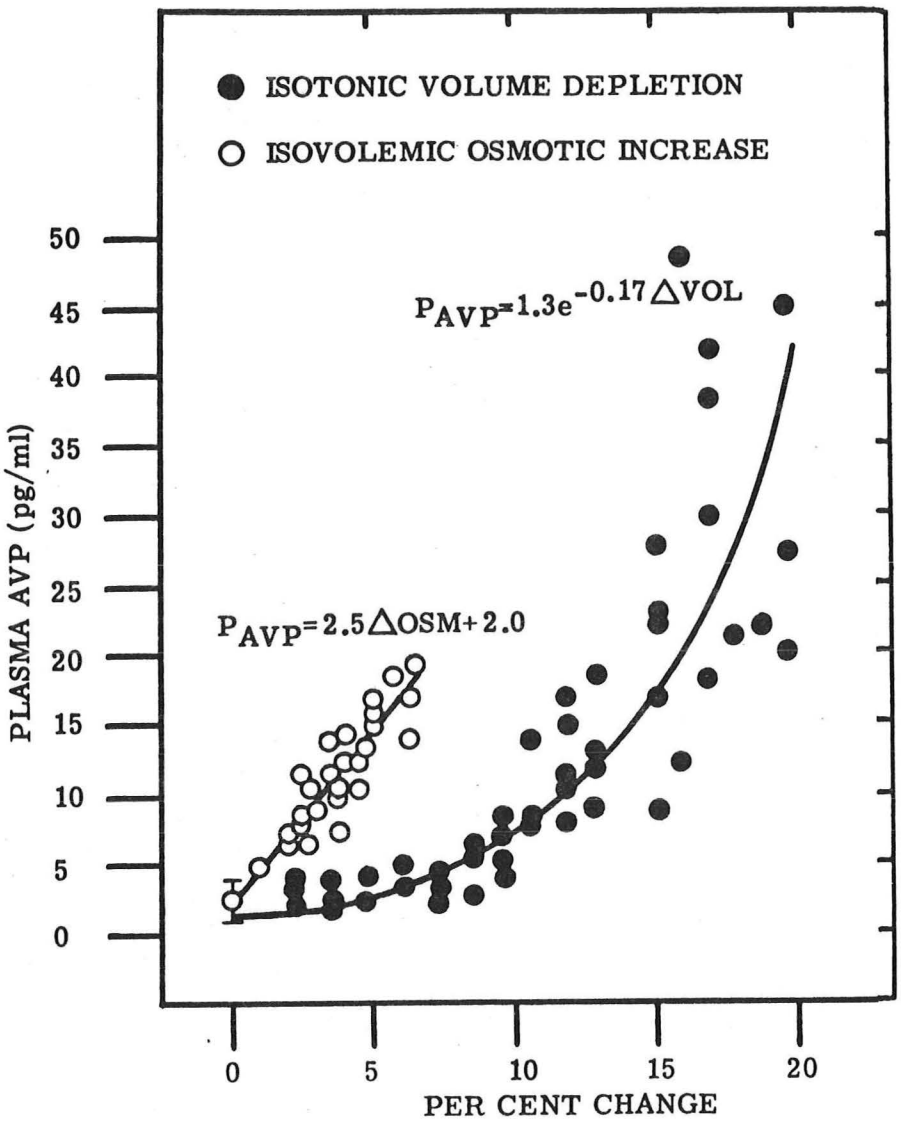

Figure 5: The relationship of plasma ADH to percent change in plasma osmolality and blood volume (22).

of 8% or more were achieved. When compared on a percent change basis, Figure 5, it can easily be appreciated that the plasma ADH levels are more sensitive to small changes in osmolality than they are to small changes in blood volume. These studies which have directly examined the relative importance in rat of the osmolality and volume control of ADH release would not be consistent with the commonly held view that volume is the

primary regulator of ADH secretion rates. Whether similar results will be obtained in humans awaits similar radioimmunoassay studies in patients with various volume and electrolyte derangements. A priori, I personally would predict that serum osmolality does not have the same degree of primacy over volume in humans as in rats since it is clear that patients in congestive heart failure and with cirrhosis (who have associated hyponatremia) may in fact have concentrated urines.

In addition to the volume and osmolar control of ADH release, a number of studies have shown that beta adrenergic stimulation with isoproproterenol is associated with antidiuresis (23-29), while alpha adrenergic stimulation with norepinephrine is associated with exaggerated diuresis (26,30-33). Neither of these stimulatory processes are associated with changes in either blood volume or osmolality and thus can be collectively referred to as "non-volume-or-osmolar" control mechanisms of ADH secretion. Both of these mechanisms are thought to be mediated through the intermediary effects of ADH.

The renal group in Colorado directed by R. Schrier has been recently studying how alpha or beta adrenergic stimulation may effect the release of ADH. They have correctly argued that these adrenergic effects may be effected through changes in blood pressure, direct action on the neurohypophyseal-hypothalamic tract, or by effects mediated through the baroreceptors. To test these alternatives a number of different types of studies were conducted. In their initial studies either isoproterenol (29) or norepinephrine (33) was infused directly into the carotid artery in a concentration that approximated those in cerebral circulation but in concentrations that were without concomitant changes in systemic glood pressure. No effect was noted with either of these adrenergic agents and thus Schrier's group concluded that cerebral arterial concentrations of the catecholamines are not responsible for direct regulation of ADH secretion (29,33). The next series of studies were designed to determine the effect of cerebral perfusion pressure on the release of ADH. In these studies the cerebral perfusion pressure was either decreased by constriction of the carotid arteries above the level of the carotid sinus (to simulate blood pressure effects of isoproterenol) or to increase the cerebral blood pressure by an exterior pump placed above the carotid sinus (to simulate norepinephrine effects). Neither of these maneuvers had any effect on the diuretic pattern of the dogs studied (29,33).

If, however, the cerebral blood pressure was either raised or lowered below the carotid sinus then the animals became respectively either diuretic or antidiuretic. Thus these studies suggested that the baroreceptors located within the carotid sinus were the responsible mediating mechanism. Thus a group of studies were conducted in animals with carotid sinus denervation or in animals which were Sham operated. In the carotid sinus denervated group the usual opposing effects of beta and alpha adrenergic stimulation on water excretion were eliminated, whereas the Sham

operated animals had the expected response to either isoproterenol or norepinephrine administration. Thus the neural tone of the baroreceptor appears to be a third major factor which regulates the secretory rate of ADH.

Etiology of Hyponatremia:

It is now well accepted that exogenously administered ADH induces natriuresis in animals who are not salt depleted (3-5). A number of hypothesis for the reasons for natriuresis have been advanced; however, no definite single mechanism has been agreed upon. It was once thought that the mild degrees of volume expansion which are assoicated with SIADH are responsible for proximal tubule inhibition of sodium reabsorption, but more recent literature would indicate that the natriuresis associated with mild states of volume expansion is a late distal or a collecting tubule effect (33-37).

Of clinical importance, however, is not the mechanism of natriuresis, but rather, is the degree of urinary salt loss enough to account for the degree of hyponatremia often seen with SIADH. Detailed balance studies are necessary to examine this issue in depth. The consensus of these types of studies is that hyponatremia results from the dilution of serum sodium from retention of water, intracellular shift of sodium, and from increased excretion of sodium.

A normal man can vary his daily intake of fluid from 0.5 to 10 liters a day without significant changes in his serum sodium concentration. However, this is not the case with patients who have the SIADH. These patients are able to maintain normal serum sodium concentrations only with adequate salt intake provided it is coupled to a restricted intake of fluids (1,38-41). This was clearly demonstrated by studies of Carter et al. (39) in which two patients with SIADH secondary to cerebral disease were examined in detail. These patients had a normal serum sodium concentration of 140 mEq/L on water restriction and moderate sodium intake. In one of their patients who was kept on a constant water intake of 2500 cc per day the serum sodium concentration decreased from 140 mEq/L to 116 mEq/L within two days when oral sodium intake was reduced from 131 to 17 mEq/day. Serum ADH levels were not measured; however, since the urine became hypertonic to serum at a time when the patients were in positive water balance, is highly suggestive that these findings were secondary to uninhibited and continued secretion of ADH (39). Nolph and Schrier (41) have similarly studied a patient with SIADH over a nine month period. Their patient maintained a normal serum sodium concentration on a diet containing 113 mEq/day sodium provided his daily intake of fluid was restricted to 20 ml/kg/day, or 1148 nl/day. With a minimal increase of fluid intake to 25 nl/day the patient gained weight and became hyponatremic. If the volume expansion was rapid, then the patient went into negative salt balance; however, during the period of gradual water expansion, the

urinary losses of sodium did not exceed the dietary intake of sodium. In both cases the patient became hyponatremia. These data clearly demonstrate that salt loss by the kidney did not contribute significantly to the pathogenesis of the hyponatremia, in fact, hyponatremic subjects with SIADH may achieve a steady state in which urinary sodium concentration is near zero if the intake of sodium is low (41). Since the development of hyponatremia is not secondary to salt wastage, it must be due to other processes. Characteristically patients with SIADH gain several kilograms of weight on nonrestricted fluid regimes; however, they do not develop clinically detectable edema. The most consistent finding has been an increase in total body water which is largely due to rises in extracellular volume compartments (1,39,42-45). The total blood volume generally is within normal range (40,45-47).

The argument put forth in the preceding paragraph would suggest that hyponatremia of SIADH is secondary to dilution as associated with increased water retention. This contention is difficult to prove or disprove due to the inherent difficulties associated with balance studies. In attempting to evaluate the published data however, it does become clear that neither sodium loss or excess fluid accumulation can completely account for the severity of hyponatremia. Studies of Kaye (48) have examined this question in detail by measuring the various fluid compartment and muscle electrolyte in 10 patients with SIADH. In contrast to other workers Kaye (48) found no change in the extracellular fluid compartment but an increase in total body water. In addition he found a significant increase in the intracellular muscle sodium concentration. He thus argued that the hyponatremia seen in SIADH may be secondary to redistribution of total body sodium into intracellular compartments. Nolph and Schrier (41) also were unable in their very long balance studies to account entirely for the degree of hyponatremia by involving purely renal losses of sodium and/or increased accumulation of water.

In summary, there are at least three fundamental causes that contribute to the development of hyponatremia: 1) net renal losses of sodium; 2) back diffusion of free water from the collecting duct resulting in increased accumulation of total body water; and 3) intracellular shift of sodium. Because of the difficulties with balance data, it is not possible to make any quantitative statements concerning the relative importance of any of the stated mechanism except that in each of the studies reviewed the renal loss of sodium must contribute very little to the overall development of hyponatremia.

Disorders Occasionally Associated with SIADH:

In 1967 Schwartz and co-workers (1) reported two patients with bronchogenic carcinoma in whom hyponatremia developed as a result of sustained inappropriate secretion of antidiuretic hormone. Both of these cases are

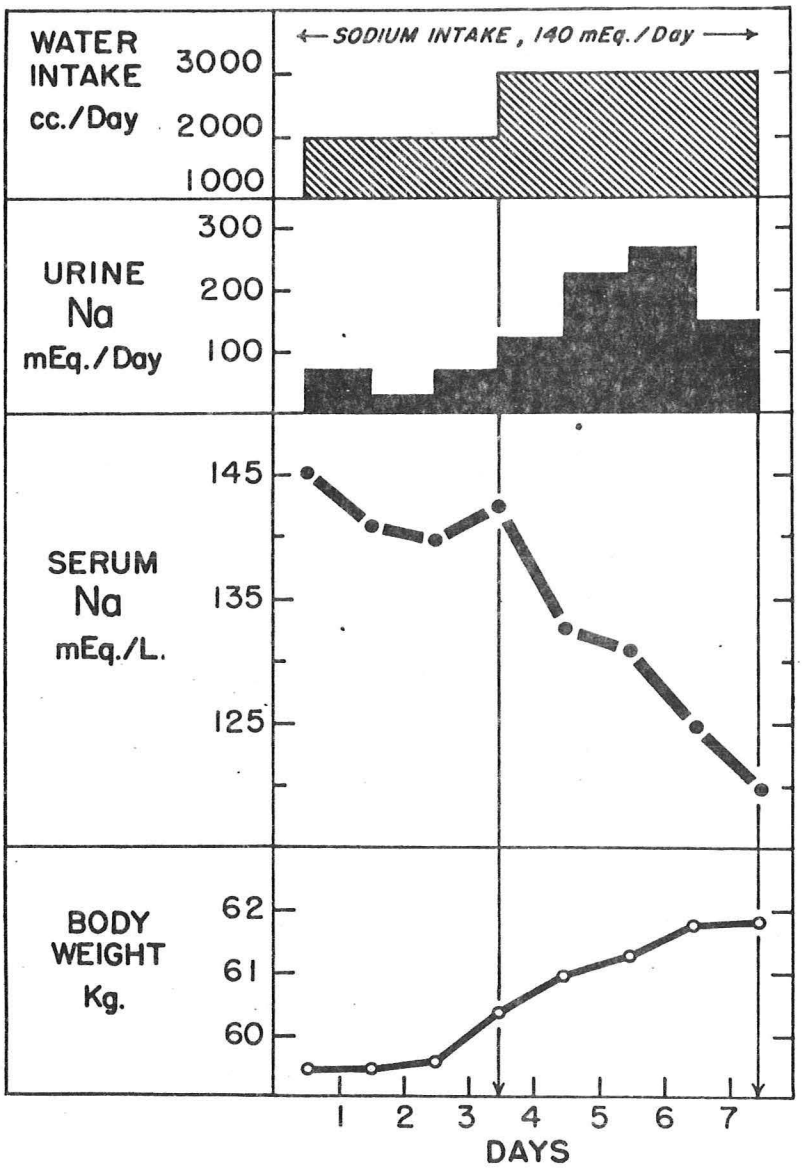

Figure 6: Seven day balance study to illustrate response of urinary sodium excretion rates, serum sodium concentration and net gain of weight to increase in daily intake of fluid from 2000 to 3000 cc in a patient with SIADH (1).

quite typical of the great number of other patients who have subsequently been reported to have SIADH (for excellent review see Schwartz and Bartter (49). Figure 6, taken from one of Schwartz's (1) index cases, illustrates many of the salient features of this syndrome. This figure is a short seven day balance study performed on a 60 y/o patient who was admitted

with a history of anorexia, weakness, fatigability, confusion and episodes of frank disorientation. Many of these symptoms were thought to be secondary to hyponatremia with serum sodium ranging as low as 105 mEq/L. The autopsy revealed a bronchogenic carcinoma. Prior to his demise, his serum sodium was brought up to normal level with moderate salt intake (140 mEq/day) and a fluid restriction to 2000 cc/day, Figure 6. On the third day of the study, fluid intake was liberalized to 3000 cc without change in the intake of sodium. Shortly thereafter the urinary sodium excretion rose, serum sodium concentration began to drop precipitously and the patient gained some two kilograms of water. All these events took place secondary to presumed inappropriately high concentration of serum ADH.

Of the various disorders associated with SIADH, "oat-cell" bronchogenic carcinoma remains the most common of the carcinogenic etiologies (49). SIADH has also been reported with carcinoma of the duodenum (49), pancreas (50) and prostate (51). In addition SIADH has been reported with Hodgkin's disease (52) and with reticulum cell sarcoma (53). In those cases which have so been examined, tumor tissue bioassays have demonstrated large quantities of ADH like material (44, 54-62). Of course the high concentration of ADH measured in the tumor tissue may be secondary to tissue "trapping" of ADH or de novo synthesis. A beautiful study has recently addressed itself to this issue. George, Capen and Phillips (63) took slices of undifferentiated bronchogenic carcinoma obtained from a 68 y/o male patient and were able to demonstrate in vitro biosynthesis of vasopressin. This report clearly demonstrates that at least a fraction of patients with SIADH in association with tumors have the syndrome secondary to ectopic biosynthesis of ADH. Thus there would be no reason to expect that its synthetic and release rate would be governed by those regulatory factors which determine the amount of ADH released by the posterior pituitary.

A number of various pulmonary diseases without malignancy have also been reported to be associated with SIADH. Of these, tuberculosis is the most common (64-68), but SIADH has also been reported with pneumonia (69,70) and with cavitary aspergillosis (71). That hyponatremia and renal salt wasting occurs with advanced pulmonary tuberculosis has been known since the original description of Winkler and Crankshaw (72); however, not until the latter part of the 1960's was this attributed to inappropriate secretion of vasopressin (65-67). The most definitive studies in this area are those of Kleeman's (68) laboratory in which his co-workers assayed the tuberculosis lung tissue of a 51 y/o patient with SIADH and found it to contain very high concentrations of ADH activity as determined by bioassay techniques. Uninvolved lung tissue from the same patient did not have antidiuretic properties. These findings thus are consistent with ectopic production of ADH.

Syndrome of inappropriate ADH secretion has also been frequently reported with various types of intracranial diseases or head injuries, for a comprehensive review see reference 49. One of the common features is that the entire SIADH is usually reversible when the underlying disease has been treated. Perhaps there exists a transient stimulation for ADH release in inflammatory basis.

In addition to the various pathophysiological states, a number of drugs have been reported to cause hyponatremia and a syndrome indistinguishable from SIADH. Among these drugs are chlorpropamide (73-75) and vincristine (76-78). Also diuretics have been shown to cause hyponatremia at a time when urine is not maximally dilute (79-81). Whether or not this represents an inappropriate secretion of vasopressin awaits further evaluation.

Treatment:

The treatment of patients with SIADH may be considered under three different categories: acute treatment of hyponatremia; chronic control of electrolyte and water metabolism; and treatment of the underlying disease causing the SIADH.

Rapid correction of hyponatremia is not indicated unless the patient has severe symptoms of water intoxication. Under normal circumstances symptoms of hyponatremia do not become manifest until serum concentrations are below 115 mEq/L and generally do not become life threatening until serum sodium concentrations fall to concentrations less than 90 mEq/L. If, however, the patient presents with severe disorientation, confusion or coma as a consequence of hyponatremia, then immediate administration of hypertonic saline infusion is indicated. It should, however, be emphasized that administration of hypertonic saline has no long term benefits, and that infusion must be continuous to raise the serum sodium concentration at all (39). The reason for this is that in the SIADH even massive doses of administered sodium are excreted immediately into the urine. However, this approach does allow for "purchase of time" and will prevent immediate dangers of severe water intoxication.

The basic treatment of hyponatremia secondary to SIADH is water restriction coupled with a moderate intake of salt. Normally this is accomplished with restriction of fluid intake to 1 liter per day with a sodium intake of about 140 mEq/day. Diuretics should not be used, in fact, these may have deleterious effects (82) and have occasionally been described to precipitate the development of SIADH.

Treatment of the underlying disease of course is the treatment of choice. Prompt improvement of the water and electrolyte disturbances have been noted with surgical resection of carcinoma or with medical treatment of the disease process responsible for the syndrome.

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