University of Texas
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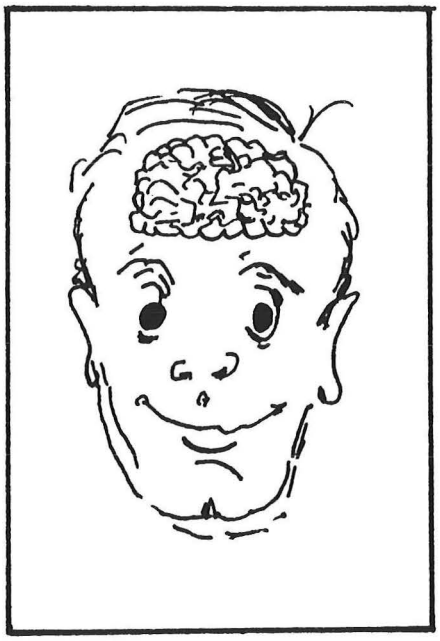
at Dallas

HYPEROSMOLAR STATES



Internal Medicine Grand Rounds

January 25, 1990

Robert Alan Star, M.D.

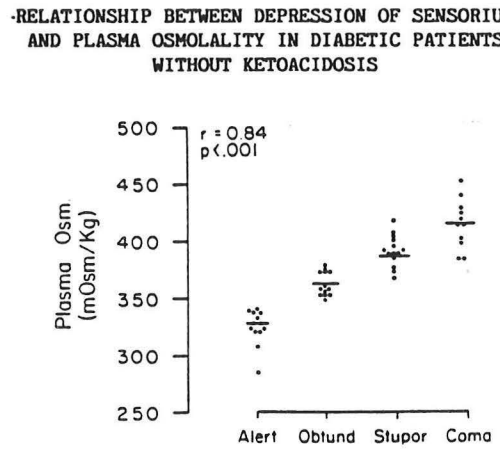
INTRODUCTION

The composition of the extracellular fluid must remain stable for proper function of most cells in the body. An elaborate network of regulatory mechanisms maintains the extracellular osmolality within a very narrow range of 280-292 mOsm/kg, despite wide variations in water intake. In hyperosmolar states, breakdown of these regulatory processes can result in serious neurologic symptoms primarily caused by water movement out of the brain.

The first case of acute hyperosmolality occurred in the dessert near Zoar. While the cities of Sodom and Gomorrah were being annihilated, Lot's wife looked backwards and became dehydrated so quickly that the salts in her body exceeded their solubility in plasma. Presumably, if she had access to water, she would not have turned into a pillar of salt (Genesis 19:26). This case illustrates several points. 1) Hyperosmolality is usually due to water loss, 2) Water loss causes hypernatremia, and 3) Thirst provides the ultimate protection against hypernatremia.

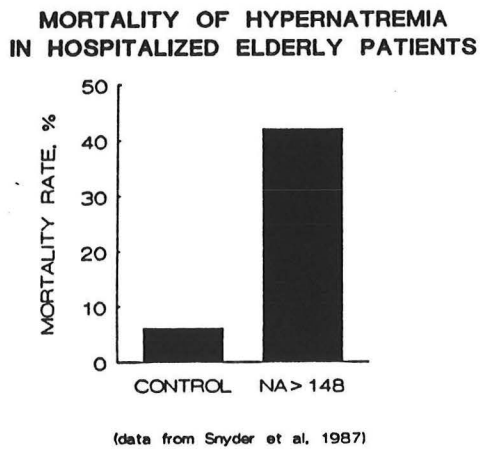
The major causes of an elevated plasma osmolality are hypernatremia, hyperglycemia, and elevated urea. Some forms of hyperosmolality are associated with significant morbidity and mortality. For example, there is a significant correlation between depression of sensorium and plasma osmolality in diabetic patients who present without ketoacidosis (Figure 1) (1).

FIGURE 1



[Ref: Arieff and Carroll, 1974]

FIGURE 2



While not the only factor, plasma osmolality greater than 340 mOsm/kg contributes to the depression of sensorium. The mortality of chronic hyperosmolar states can be substantial. For example, the mortality rate of hospitalized elderly patients with hypernatremia (Na > 148) was 42%, seven times the mortality rate for age-matched control patients (Figure 2) (2).

PHYSIOLOGY OF WATER BALANCE

The osmolality of body fluids is determined by the ratio of total body solute to total body water:

$$\text{OSMOLALITY} = \frac{\text{TOTAL BODY SOLUTE}}{\text{TOTAL BODY WATER}}$$

Since the solute content of the body is usually stable, the osmolality of body fluids is primarily determined by changes in total body water. Total body water is determined by the rate of intake (drinking) and the rate of loss of water primarily via the urine.

Separate control mechanisms regulate oral water ingestion and renal water excretion **(Figure 3)**. Dehydration sufficient to increase plasma osmolality is sensed by osmoreceptors which cause secretion of arginine vasopressin (AVP; also known as antidiuretic hormone or ADH), and also induce thirst. The resulting renal water reabsorption limits further water loss, while water ingestion restores plasma osmolality back to normal.

FIGURE 3

DUAL CONTROL OF PLASMA OSMOLALITY

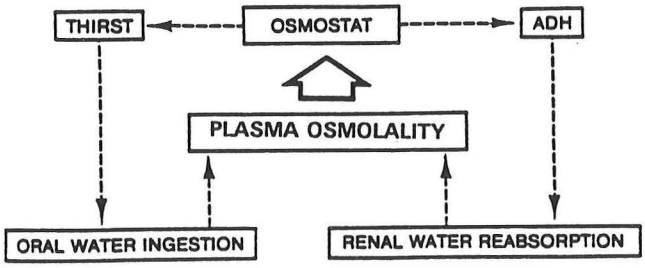
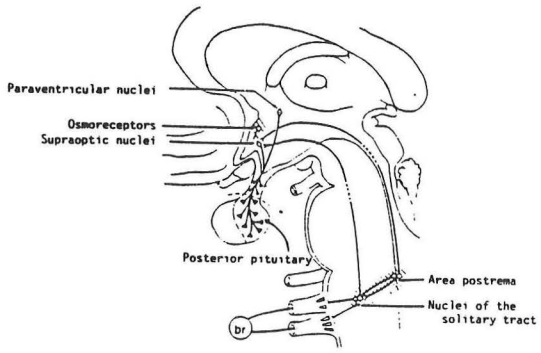


FIGURE 4

LOCATION OF VASOPRESSIN PATHWAYS



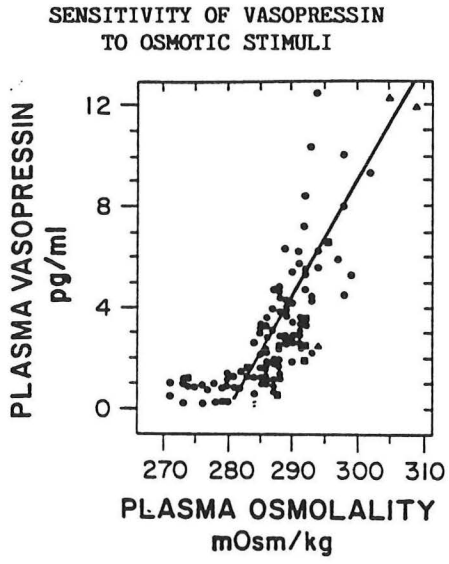
Modified from Robertson and Berl, 1986

Secretion of Arginine Vasopressin (AVP). The AVP feedback loop involves two anatomic sites: brain and kidneys. Figure 4 shows the location of the important AVP pathways.
AVP is synthesized primarily in the supraoptic and paraventricular nucleus of the anterior hypothalamus, stored within granules bound to a specific carrier protein called the neurophysin, and transported along the axon into the posterior pituitary (3). A single mRNA encodes for both the neurophysin and AVP (4). AVP is normally released in response to osmotic stimuli provided by osmoreceptors thought to reside in the organum vasculosum of the lamina terminalas region of the anterior hypothalamus (5,6). Since this region of the brain has large gaps or fenestrations in the blood brain barrier, the osmoreceptors have direct access to plasma (reviewed

in (6)). AVP is also released in response to baroreceptor information (3,6). Pressure sensitive receptors in the cardiac atria and carotid sinuses travel via the vagal and costophrenic nerves to the nuclei tractus solitarius in the brain stem. These signals are carried by noradrenergic pathways to the hypothalamus (3).

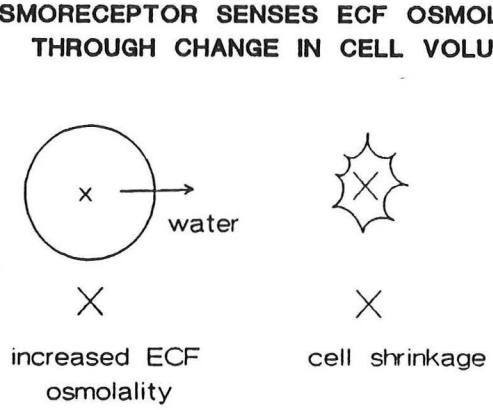
Figure 5 shows the relationship between plasma osmolality and plasma AVP concentration (7).

FIGURE 5



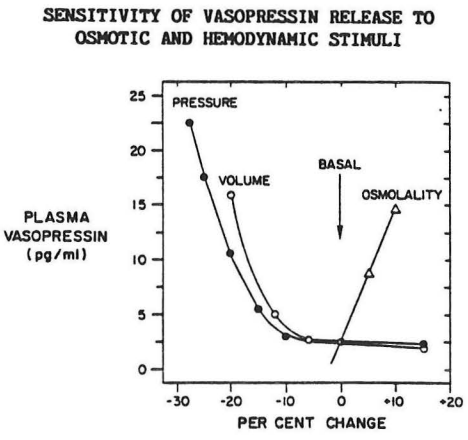
[Modified from Robertson and Berl, 1986]

FIGURE 6



When plasma osmolality is less than 280 mOsm/kg, circulating levels of AVP are undetectable, while above 282 mOsm AVP increases linearly. Osmotic control of AVP is so sensitive that a 1-2% change in plasma osmolality is sufficient to evoke a readily detectable change in plasma AVP (7). While the exact stimulus for release of AVP is unknown, Verney (Figure 6) suggested that osmotic shrinkage of osmoreceptor cells regulates AVP release (8). Elevation of plasma osmolality causes movement of water from the osmoreceptor into the extracellular space, resulting in cell shrinkage. AVP release is coupled to cell shrinkage by unknown mechanisms.

FIGURE 7



[Ref: Robertson and Berl. 1986]

Changes in blood volume and blood pressure also have important effects on ADH release (Figure 7); however, blood volume must decrease 7-10% before AVP is released (9). This mechanism functions to preserve blood volume by limiting renal water excretion during extreme hemodynamic stress such as blood hemorrhage.

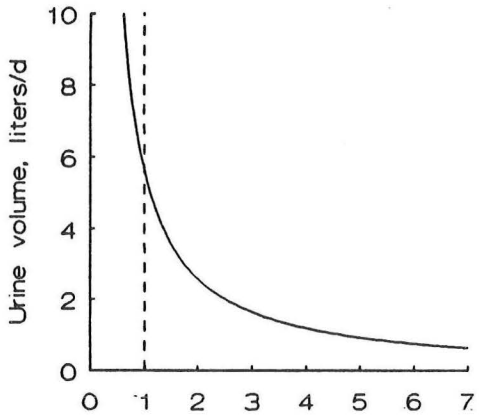
AVP is inhibited by drinking fluids. For example, sucking on ice chips for 30 minutes promptly decreases plasma AVP levels before changes in extracellular fluid volume or osmolality are detectable (10). This is thought to occur by activation of cold-sensitive oropharyngeal receptors (10,11) or swallowing reflexes (12).

In addition to the physiological stimuli, other stimuli (nausea for example) influence ADH release which have no obvious homeostatic role and which can take precedent over the usual physiological stimuli (7).

<u>Control of Renal Water Excretion by Arginine Vasopressin (AVP)</u>. The second anatomic site which regulates body water balance is the kidney. Figure 8 which shows the effect of plasma AVP on urine volume. When plasma AVP levels are undetectable (<1 pmol/l), the kidney excretes >10 liters/day of very dilute urine. Conversely, once plasma AVP becomes 5 or greater, the kidney excretes a very concentrated urine in a volume of approximately half to 1 liter/day. The gain of the system is so high that a change in plasma osmolality of 1 mOsm is sufficient to raise urine concentration by 100 mOsm/kg, a gain of 100 fold.

FIGURE 8

RELATIONSHIP BETWEEN URINE VOLUME AND PLASMA AVP IN HEALTHY ADULTS



Adapted from Robertson et al., 1982 and Baylis, 1987

FIGURE 9

VASOPRESSIN RESPONSIVE SITES

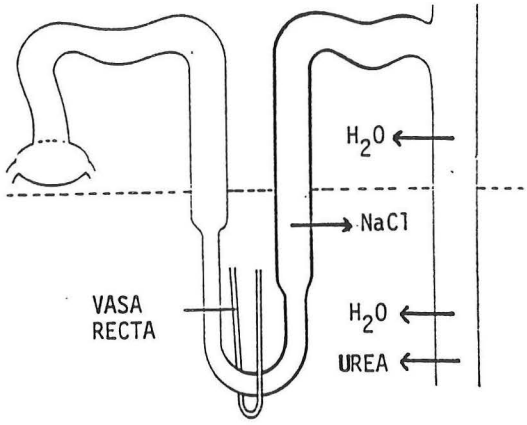


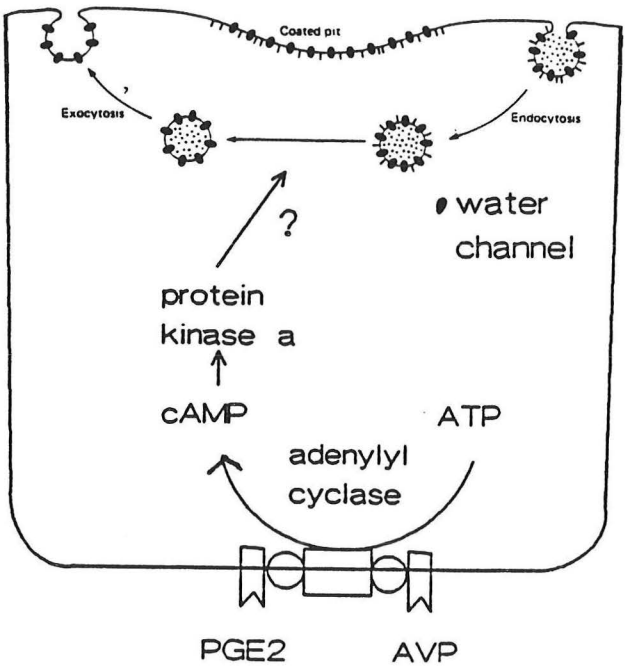
Figure 9 shows the AVP-responsive sites of the nephron that are important for renal water conservation. Approximately 66% of the water filtered at the glomerulus is absorbed by the proximal tubule and loop of Henle by mechanisms which are largely independent of AVP. At the end of the thick ascending limb, the luminal contents are dilute (~100 mOsm/kg). If the collecting duct system were made largely impermeable to water as occurs in the absence of AVP, most of these 20-30 liters would be excreted by the kidneys. AVP acts at four sites to decrease renal water excretion. AVP maximizes the osmotic gradient across the collecting duct by enhancing sodium chloride transport in the thick ascending limb which increases the interstitial salt concentration (13), and by decreasing blood flow to the vasa recta which keeps the salt in the medulla (13). AVP increases

the water permeability of the collecting duct allowing water absorption down its concentration gradient from lumen to interstitium (14). Urea is very important in the renal concentrating mechanism (15). AVP increases urea permeability of the inner medullary collecting duct, preventing urea which has been concentrated in the lumen by water abstraction, from retarding water abstraction (16-19).

The mechanism by which AVP increases the water permeability of a collecting duct principle cell is shown in Figure 10. In the absence of AVP, the apical membrane is the barrier to water absorption across the cell (20). AVP increases the water permeability of the apical membrane by binding to a V2 receptor in the basolateral membrane, which activates adenylyl cyclase through a G-protein mechanism, generating cAMP (21). Through a series of intermediate steps, the apical membranes are made water permeable by insertion of a water channel (22-26).

FIGURE 10

AVP INCREASES APICAL MEMBRANE WATER PERMEABILITY IN COLLECTING DUCT



Thirst. AVP by itself cannot stabilize plasma osmolality since maximal urine concentration still obligates about 1/2 liter of water loss a day. A mechanism is necessary to promote fluid intake, i.e., thirst. Serious study of thirst is hampered by the subjective nature of thirst (12). Thirst can be defined as a deep-seated sensation of a desire for water which causes a powerful behavioral drive to drink water. As with AVP secretion, thirst is influenced primarily by osmotic and hemodynamic factors, suggesting that both AVP and thirst share the same osmoreceptors (27) (Figure 11).

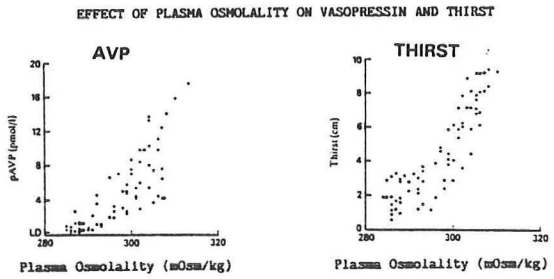
FIGURE 11

CONTROL OF THIRST

PHYSIOLOGIC
- Plasma osmolality
- Decreases in blood volume and pressure
- Drinking

PATHOPHYSIOLOGIC
- reset upward by volume expansion and opiates

FIGURE 12



[Ref: Thompson et al., 1986]

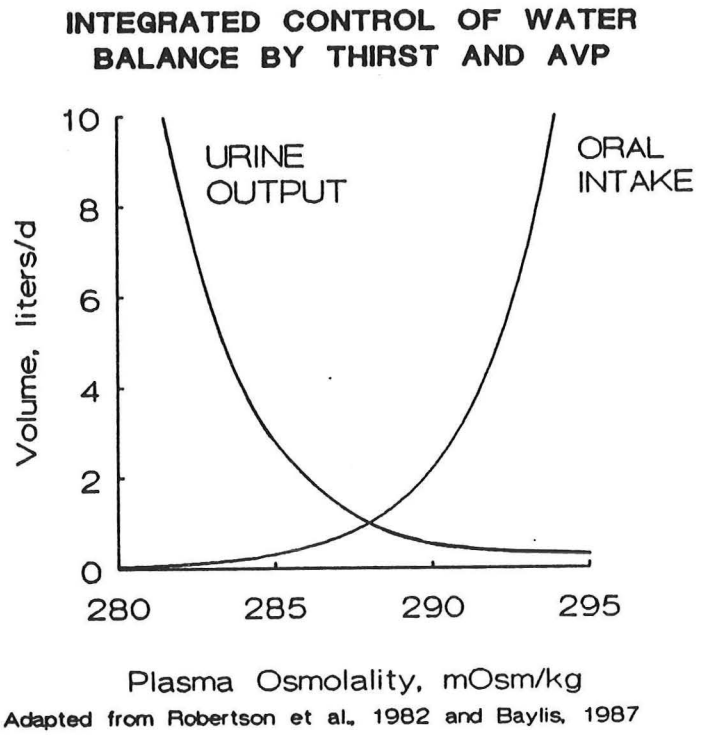
However, one patient has totally intact AVP release but lacks any appreciation of thirst (28). Therefore at least some of the osmoreceptor input is anatomically separate, a hypothesis which is supported by animal models (12). Thirst osmoreceptors are thought to be located in the anterior ventral third ventricular region and sub-fornical organ (3). In earlier studies of osmoregulation, thirst was considered to be either present or absent. Using this definition, thirst was experienced only at plasma osmolality greater than 195 mOsm/kg; i.e., a level associated with a maximal AVP-induced antidiuresis (7). Thus, the thirst mechanism was assumed to operate only when AVP contributed no further to the stability of plasma osmolality (29). However, the exquisite sensitivity of thirst to osmotic stimuli has been documented only in the past few years (Figure 12). By using a continuous visual analog scales to semi-quantitatively estimate thirst during osmotic stimulation (12,30,31), it has been shown that the intensity of thirst varies with the degree of osmotic stimulation and is clearly experienced at plasma osmolalities below the level associated with maximal antidiuresis (12,31). The osmotic threshold for thirst and AVP release are similar in healthy men (31). While there is a wide variation in the sensitivity to thirst among individuals, there is remarkable consistency within an individual over time (31).

Drinking after water deprivation rapidly decreases thirst before plasma osmolality changes (10,11,32-34). The mechanism of this rapid satiation of thirst is unknown; both cold sensitive oropharyngeal receptors (10) and swallowing-mediated neuroendocrine reflex (12) have been proposed. The former may explain why patients with diabetes insipidus or severe dehydration desire cold liquids.

Angiotensin II plays a major but not exclusive role mediating the osmotic stimuli for thirst in laboratory animals (35-37). However, the role of angiotensin II in humans is unclear. For example, thirst occurs following severe hypovolemia or hypotension but rarely with more modest reductions in blood pressure or blood volume. For example, standing does not produce a predictable increase in thirst despite a decrease in central blood volume sufficient to increase AVP secretion and plasma renin activity (30). Renal artery stenosis fails to increase thirst although it does dramatically activate the renin angiotensin system. These observations suggest that humans are not as sensitive to angiotensin II as laboratory animals (38).

Integrated Control of Water Balance. Together, AVP and thirst maintain plasma osmolality within a narrow range (Figure 13).

FIGURE 13



Overnight dehydration sufficient to raise plasma osmolality by 3-5 mOsm/kg increases plasma AVP which limits renal water loss. At the same time, thirst increases and eventually leads to water ingestion. Drinking rapidly abolishes thirst, preventing water intoxication. Absorption of the ingested water restores osmolality to normal. Thus, the thirst mechanism is the major defense against dehydration. An intact thirst mechanism is extremely important in patients with diabetes insipidus, who excrete 20 liters of urine daily. These patients have normal or only slightly elevated plasma osmolalities as long as they are awake and alert. However, loss of consciousness (during surgical anesthesia for example) can cause rapid dehydration and hypernatremia unless water loss is prevented (AVP) or replaced(D5W). Thus, plasma osmolality can be successfully regulated without an effective renal concentrating mechanism as long as the thirst mechanism is intact and the access to water is unrestricted. The only contribution of the renal concentrating mechanism is to lessen the dependence on a thirst mechanism and the need to remain close to a water supply and a bathroom.

Actually, the major role of AVP is to prevent water intoxication. Water ingestion decreases plasma osmolality subsequent suppression of AVP secretion allows maximal renal water excretion. Thus, as long as the kidneys are working and AVP is suppressed, it is nearly impossible to become water intoxicated.

PATHOPHYSIOLOGY

Hyperosmolality can be generated either by unreplaced water loss or acute addition of solute to the extracellular space. Since the most important predictor of the associated clinical symptoms is the ability of the disturbance to shrink cells, we shall consider the effects of extracellular water loss and extracellular solute gain on cell volume.

Water normally comprises about 60% of body weight, about 45 liters in the normal 75 kg patient. Two-thirds of the water or 30 liters are inside cells whereas 1/3 of the water or 15 liters is extracellular (Figure 14).

FIGURE 14

WATER LOSS IS DISTRIBUTED THROUGHOUT TOTAL BODY WATER

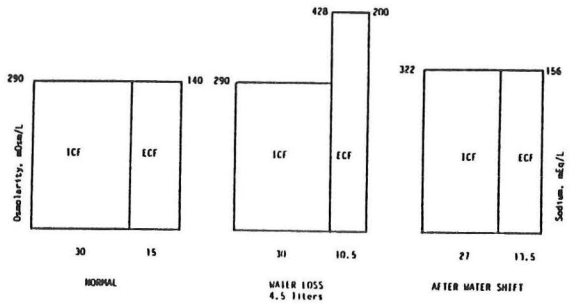
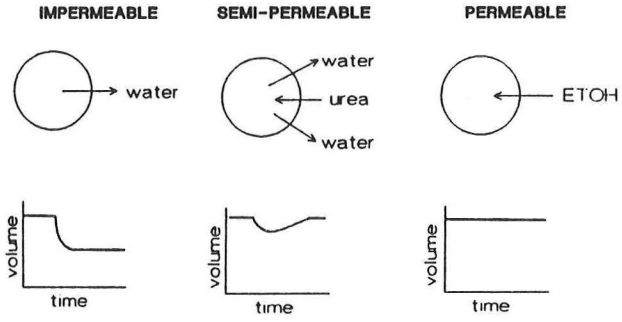


FIGURE 15

EFFECT OF ACUTE SOLUTE ADDITION DEPENDS ON PERMEABILITY OF CELL



Since most cell membranes are permeable to water (exceptions are the apical membrane of the cells in the collecting duct and sweat ducts), the osmolality will be equal in both compartments, i.e. 290 mOsm/kg which is equivalent to a sodium concentration of 140 mEq/L. A water loss of 10% of body water or 4.5 liters will be limited initially to the extracellular fluid, increasing ECF osmolality to 428 mOsm/kg. However, the ECF to cell osmolality gradient will drive water flow from cell to ECF until osmotic equilibrium occurs. If the total amount of solute in the body is constant, the final sodium concentration will be 156 mEq/L. Thus, water loss from the body causes cell shrinkage and increases cell osmolality. Furthermore, since sodium is the most prevalent ECF solute, unreplaced water loss causes hypernatremia.

The effects of solute addition are more complicated (Figure 15). The extent of cell shrinkage following addition of solute to the ECF depends on the ability of the solute to enter cells. Addition of impermanent solutes (sodium chloride, mannitol or raffinose) causes cells to shrink. In theory, the cells act as perfect osmometers, i.e. a balloon whose volume is completely controlled by the concentrations of solute inside and outside the cell. At equilibrium, cell and ECF osmolality will be equal. In contrast, addition of the semi-permeable solute (urea) initially causes shrinkage of cells. However, as urea enters the cell and raises internal osmolality, cell volume with return to a baseline volume as the urea concentration within the cell becomes equal

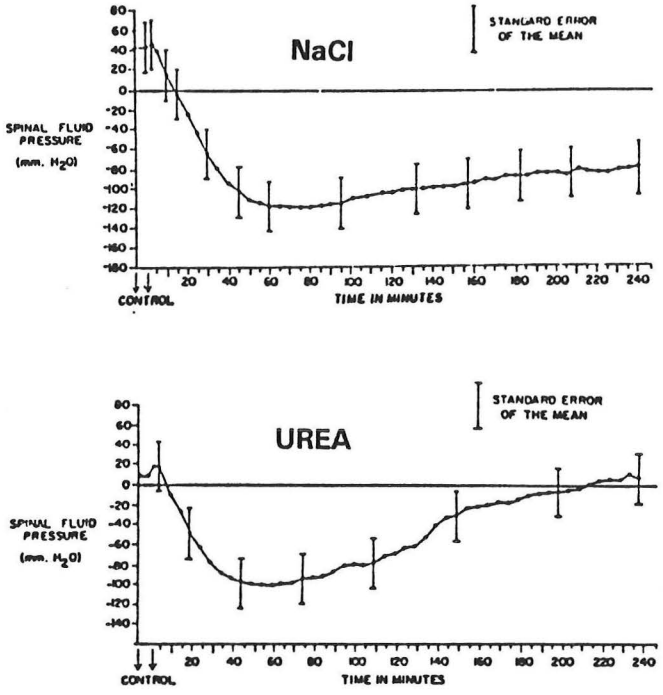
with virtually no change in cell volume. In all three cases, cell and ECF osmolality will be equal in the steady state.

Figure 16 shows the effect of rapid infusion of concentrated NaCl and urea on CSF pressure (39). The blood-brain-barrier is impermeable to NaCl, but semi-permeable to urea (40). NaCl causes rapid and sustained shrinkage of brain cells which decreases CSF pressure as the brain shrinks away from the rigid walls of the skull by 3-6 mm (39,41). In contrast, infusion of urea initially causes similar shrinkage of brain cells, but diffusion of urea into the brain equalizes brain and ECF urea concentration within about 4 hours (42), allowing CSF pressure to return to normal (39). It is of interest that infusion of concentrated NaCl causes sustained stupor, while urea infusions causes transient stupor which completely resolves in 4-6 hours (41,43). The blood-brain-barrier permeability can account for differences in the clinical symptoms (39).

<u>The concept of effective osmolality or tonicity</u>. Since the most important predictor of clinical symptoms in hyperosmolar states is the ability of the solute to shrink cells, solutes are divided into two classes (Figure 17).

FIGURE 16

EFFECT OF NaCl AND UREA ON CSF PRESSURE IN CATS



[Ref: Luttrell et al., 1959]

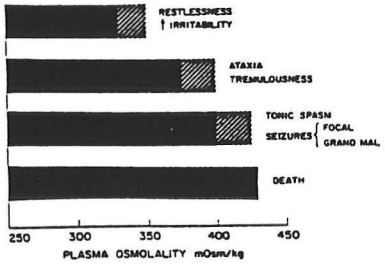
FIGURE 17

CLASSIFICATION OF SOLUTES: CONCEPT OF EFFECTIVE OSMOLALITY AND TONICITY

PERMEABILITY	**Impermeable**	**Permeable**
ABILITY TO SHRINK CELLS	**Effective**	**Ineffective**
EXAMPLES	**NaCl** **Glucose** **Mannitol**	**Alcohols** **Urea**
CLINICAL SYNDROME	**Hypertonicity**	**Intoxication** **Uremia**

FIGURE 18

EFFECT OF ACUTE HYPERTONICITY PRODUCED BY NaCl, SUCROSE OR MANNITOL INFUSIONS IN CATS



[Data from Sotos et al, 1960]

Solutes that can osmotically extract water from cells (NaCl, glucose, mannitol) are called effective solutes or effective osmoles. Solutes that enter cells so quickly that cell volume remains unchanged are called ineffective solutes or ineffective osmoles (ethanol, ethylene glycol, other alcohols, and urea). While effective and ineffective osmoles raise the measured plasma osmolality (hyperosmolality), only effective osmoles cause sustained water shifts into or out of cells (hypertonicity). This distinction in useful clinically. Ingestion of alcohols (ethanol, ethylene glycol) produces a characteristic syndrome (intoxication, metabolic acidosis) whose features are determined by inhibition of specific enzymes rather than movement of water or direct effects of hyperosmolality. Accumulation of urea produces a different but characteristic syndrome (uremia). While the uremic toxin is still unidentified, the uremic syndrome is not produced by shifts of water, so uremic patients are hyperosmolar, but not hypertonic. However, urea can behave transiently as an effective osmol if ECF urea changes rapidly. This occurs clinical only during urea infusions (no longer used for sickle cell crisis), or dialysis (either initiation of dialysis in a very uremic patient, or perhaps during high-flux dialysis).

On the other hand, elevation of plasma <u>tonicity</u> by infusion of concentrates NaCl, NaCl plus $NaHCO_3$, sucrose or mannitol produces the same clinical syndrome irrespective of the solute (Figure 18) (41). Initially the animals appeared thirsty. Once Posm rose above 350 mOsm/kg, the animals developed restlessness alternating with decreased responsiveness, ataxia, mystagmus, irregular twitching, violent trembling and finally death by respiration failure (41). Similar syndrome occurs in infants and adults (44-46).

The osmolality that determines water flow across cell membranes, effective osmolality, is approximated from the concentrations of impermanent solutes. The major impermanent solutes in plasma are sodium and its associated anions; glucose is included in this formula because the presence of hyperglycemia implies that insulin is relatively deficient. The formula for effective osmolality (E_{osm}) or tonicity is:

$$E_{osm} = 2\ Na + glucose/18.$$

If mannitol or glycerol are known to be present, they should be included. The normal range for Eosm is 275-290 mOsm/kg.

The remainder of this grand rounds will discuss hypertonic disorders.

DIFFERENTIAL DIAGNOSIS: HYPERTONICITY

Thirst provides the ultimate defense against hypertonicity. A normal thirst mechanism can keep up with nearly any rate of water loss in an awake patient with adequate access to water. However, an abnormal thirst mechanism or limited access to water is sufficient to cause hypertonicity (and hyperosmolality) because of unreplaced urinary and insensible losses, and is necessary to maintain a chronic hypertonic state initiated by another cause (water loss, solute gain). In summary, **failure to drink water is both necessary and sufficient to cause chronic**

hypernatremia. Based on these considerations, patients with hypertonicity can be classified by asking two questions:

Why isn't the patient drinking?

Is the hypertonicity exacerbated by excess water loss or solute gain?

Inadequate Intake of Water (Figure 19). Inadequate intake of water for whatever reason will cause hypernatremia, because sodium is major extracellular cation. Patients in coma or with decreased levels of consciousness either do not sense thirst or are unable to communicate their thirst. Some patients can sense thirst but water is unavailable (deficient supply of water, for example an ocean or dessert) or restricted (physical immobility or immobilizing restraints). The later case is commonly seen at extremes of age: very young or very old. Hypernatremia is very rare in conscious patients who are allowed free access to water because of the exquisite sensitivity of the thirst mechanisms. While the objective measurement of thirst is difficult, the clinical assessment is quite straightforward. A thirst defect is present if an awake patient with chronic hypernatremia does not complain of thirst, or does not drink water placed at the bedside. Upward resetting of the thirst threshold is seen with chronic volume expansion (primary hyperaldosteronism) which increases the osmotic threshold for thirst and AVP release; treatment with diuretics or removal of the tumor normalizes the plasma osmolality (47). Large doses opiates also elevate the osmotic threshold for AVP release; similar affects on the thirst mechanism has been postulated (7).

FIGURE 19

CAUSES OF DECREASED WATER INTAKE

Coma, decreased consciousness

Limited access to water (deficient supply, restricted access)

Hypodipsia

Volume expansion:	1° hyperaldosteronism
Pharmacologic:	opiates
Osmoreceptor destruction:	with defects in AVP secretion
	isolated hypodipsia

FIGURE 20

SPECIFIC CAUSES OF ADIPSIC HYPERNATREMIA

VASCULAR (15%)
- Anterior communicating artery aneurysms
- Intrahypothalamic hemorrhage, internal carotid ligation

NEOPLASTIC (50%)
- Primary craniopharyngioma, pinealoma, meningioma, chromophobe
- Metastatic from lung, breast

GRANULOMATOUS (20%)
- Histocytosis, sarcoidosis

MISCELLANEOUS (15%)
- Hydrocephalus, ventricular cyst, trauma, idiopathic

(from Robinson, et.al., 1982)

The most interesting but least common cause of decrease water intake usually occurs with structural lesions in the anterior hypothalamus (28,48-51) (reviewed in (6,30,38)). Because the areas which regulate AVP release and thirst overlap, defects in thirst are usually associated with relative defects in AVP. Direct damage to the osmoreceptors per se is suggested because these patients have defects in thirst and osmotically simulated AVP release but normal release of AVP to nonosmotic stimuli. If the AVP and thirst systems are reset in parallel, the patients will have a chronically elevated plasma sodium; however, they will respond normally to water load by excreting dilute urine (50,52). Two patients have been described with upward resetting of the

thirst and AVP threshold; they do not become thirsty until the plasma sodium is greater than 145-150 (see (53)). In some patients, there is complete ablation of the AVP and thirst centers. AVP is randomly secreted with intact response to hemodynamic stimuli. Therapy is extremely difficult because hyponatremia can occur following excess water ingestion. The rarest disorder is that of isolated hypodipsia with normal osmoregulation of AVP (28); the patient treated by scheduling water intake. Most of these disorders are caused by intracranial lesions in the area of the anterior hypothalamus (Figure 20); some of the patients have other associated hypothalamic or pituitary function abnormalities. Some patients have no detectable structure lesion (28,53).

Water Loss (Figure 21). Water loss rarely, if ever, is sufficient to cause hypernatremia if thirst is normal; a defective thirst mechanism is necessary for sustained hypernatremia. The classification scheme is based on the composition of the lost fluid, and its effect on ECF volume. Loss of water in excess of solute occurs through the skin or GI tract. However, the most dramatic cause of is excess of sodium water loss is via the kidneys during osmotic diuresis. The associated salt loss ($\approx$1/2 NS) causes loss of ECF volume. This occurs most commonly by glucose in uncontrolled diabetes mellitus. Euvolemic water loss (i.e., pure water) hyperventilation, but this rarely causes hypernatremia alone. The most dramatic cause of pure water loss is diabetes insipidus (DI). Urine volumes of 10-20 liters/day are seen in DI due to lack of sufficient AVP release (central DI) or inability of the kidneys to respond to AVP (nephrogenic DI). A circulating vasopressin use has ben found in a few women with transient DI during late pregnancy which can be treated with DDAVP (this AVP analogue resists degradation by vasopressin) (54). Differentiation between the two forms of polyuria (osmotic diuresis vs diabetes insipidus) is rarely difficult clinically. The solute responsible for the diuresis can be determined either by dipstick (glucose) or by clinical setting, i.e. neurosurgical ICV (mannitol, glycerol). Urine osmolality will be $\approx$300 during an osmotic diuresis, but will be low in DI.

FIGURE 21

EXCESS WATER LOSS

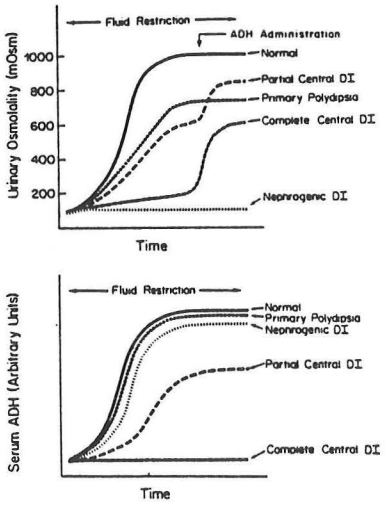
WATER LOSS IN EXCESS OF SODIUM LOSS
- Skin loss (burns, fever, sweating)
- GI loss (diarrhea, vomiting, fistulae)
- Renal loss (osmotic diuresis)

PURE WATER LOSS
- Increased insensible loss (hyperventilation)
- Renal loss
  - Central diabetes insipidus
  - Nephrogenic diabetes insipidus
- Vasopressinase
- Rhabdomyolysis

HYPERNATREMIA DEVELOPS ONLY IF THIRST IS IMPAIRED OR ACCESS TO WATER IS LIMITED

FIGURE 22

USE OF STANDARD DEHYDRATION TEST TO DIAGNOSE CAUSE OF POLYURIA



[Ref: Saxton and Seldin, 1986]

The type of DI (central or nephrogenic) can be localized using a standard dehydration test (Figure 22). The figure also shows compulsive water drinkers (primary polydipsia); however, patients with primary polydipsia who ingest 20 liters of water/day were also present with polyuria, however, they will not be hypernatremic, their plasma sodiums in general will be slightly lower than normal. The patient is fluid restricted until the urine osmolality is stable for 3 successive hourly determination or the patient loses 3-5' of body weight. Plasma osmolality and AVP are drawn, and 5 units of aqueous AVP is given by intramuscular injection. Several more urine collections are obtained. In normals, the urine becomes maximally concentrated during the period of fluid restriction (generally requiring 12-16 hrs) with no further increase in urine osmolality subsequent to AVP administration. Patients with complete central DI will concentrate their urine osmolality to about 200 by AVP independent mechanisms (55); administration of AVP will cause the urine osmolality to increase to about 600 mOsm/kg. Higher levels are not achieved because the polyuria before the test washes out the renal medulla, preventing rapid development of a maximally concentrated urine (56). The maximal urine osmolality depends on the degree of polyuria in the 24 hr before the test (57). Patients with partial central DI with low circulating AVP levels will respond appropriately to dehydration although they will not achieve maximal urinary concentration due to diminished secretion of AVP.

The standard dehydration test based on urine osmolalities has two problems: 1) any cause of chronic polyuria reduces the maximal concentrating ability (56), 2) AVP deficiency increases renal sensitivity to AVP, perhaps by up regulation of AVP receptors (29,57), and 3) almost all patients with central DI retain some ability to secrete AVP (29). It is often difficult to distinguish partial central DI from primary polydipsia or even occasionally complete central DI (57). However, assay of serum AVP has helped dramatically in correctly classifying these patients. Patients with nephrogenic DI or primary polydipsia will respond normally, patients with partial central DI will have lesser increases in AVP concentration, and patients with complete central DI will have undetectable serum ADH levels. It is essential to make the correct diagnosis. HCTZ reduces urine volume by an AVP-independent mechanism in partial central DI (58), but would cause severe hyponatremia in a patient with primary polydipsia because of the HCTZ induced diluting defect.

<u>Causes of Acute Solute Gain (Figure 23)</u>. In the presence of an intact thirst mechanism, these disturbances will be transient because water ingestion will restore plasma osmolality back to normal and the excess solute will be excreted into the urine. There are case reports of inadvertent administration (59,60) (by the intravenous route, during saline abortion, dialysis against the hypernatremic dialysate) or accidental ingestion (in chicken soup or infant feedings) of sodium chloride (61-63). Two tablespoons of salt (60 gm) contains 1 mole of NaCl, enough to raise the plasma Na by 24 mEq/L. Administration of large amounts of sodium bicarbonate during therapy for metabolic acidosis can also cause hypernatremia.

FIGURE 23

CAUSES OF ACUTE SOLUTE GAIN

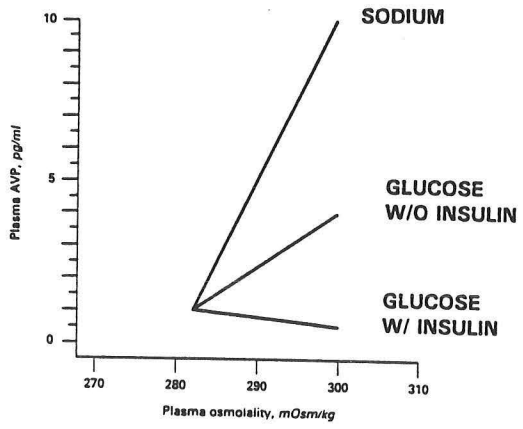
NaCl	inadvertent administration dialysis against hypernatremic dialysate accidental ingestion - chicken soup
$NaHCO_3$	during arrest, therapy for metabolic acidosis
Glucose	diabetes
Mannitol	brain edema prophylaxis

HYPERTONICITY DEVELOPS ONLY IF THIRST IS IMPAIRED OR ACCESS TO WATER IS LIMITED

Control of plasma tonicity during hyperglycemia. Poorly controlled diabetes mellitus with hyperglycemia is a common clinical problem. The pathophysiology of glucose metabolism, hyperglycemia and ketoacidosis have been reviewed at these grand rounds previously. I will focus instead on disorders in water balance that occur during hyperglycemic nonketotic hyperosmolar coma. This syndrome is characterized by extreme hyperglycemia (plasma glucose >600 mg%) and hyperosmolality (plasma osmolality >350 mOsm/kg) without significant ketonemia but with depression of sensorium (64). Insulin changes glucose from an ineffective osmole to an effective osmole, as best illustrated by the response of the osmoreceptor to glucose infusion (Figure 24).

FIGURE 24

INSULIN CHANGES GLUCOSE FROM AN INEFFECTIVE OSMOLE TO AN EFFECTIVE OSMOLE



[Ref: Robertson, 1987]

FIGURE 25

DETERMINANTS OF PLASMA TONICITY DURING HYPERGLYCEMIA

SOLUTE GAIN: Elevated plasma glucose

WATER LOSS: osmotic diuresis

THIRST: ↑ by volume depletion and ?? hyperglycemia

NORMAL THIRST MECHANISM PREVENTS HYPERTONIC STATE UNTIL PATIENT BECOMES TOO WEAK TO DRINK WATER

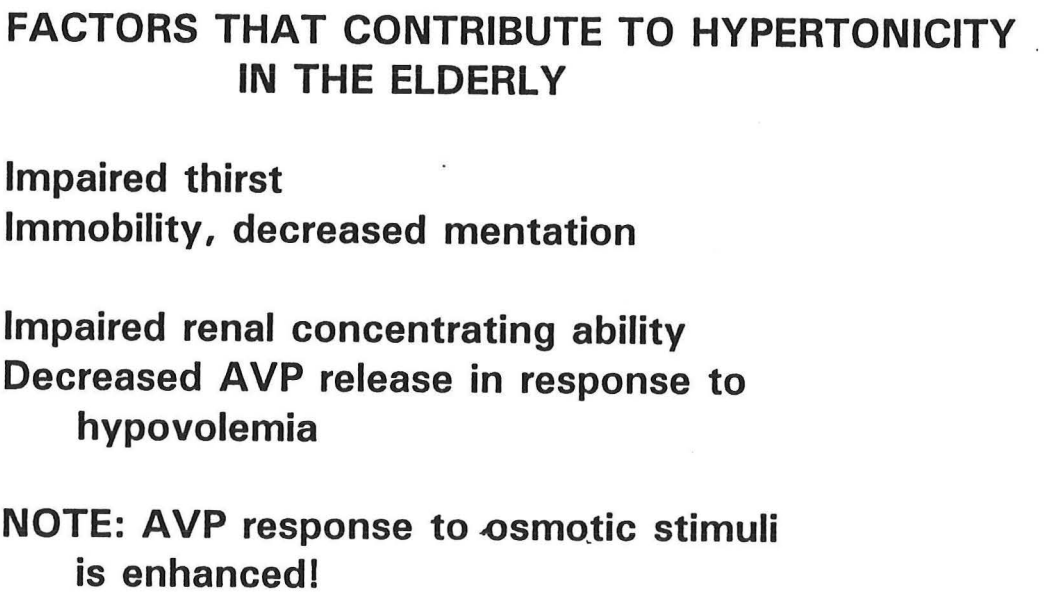
In the presence of insulin, glucose enters cells rapidly. However, in the absence of insulin glucose is excluded from most cells in the body including the osmoreceptor. This explains why infusions of concentrated glucose increases plasma AVP in the absence, but not in the presence of insulin (65-68). Figure 25 shows the determinants of plasma

tonicity during hyperglycemia. Accumulation of glucose in the extracellular fluid increases the osmolality (and tonicity) of the extracellular fluid. The increased effective osmolality causes osmotic abstraction of water from cells which increases the extracellular fluid volume and leads to hyponatremia (64). Those cells which are impermeable to glucose in the absence of insulin such as muscle will shrink. On the other hand, cells which are permeable to glucose even in the absence of insulin will swell (69). The most important example of the later is brain cells.

The expected degree of hyponatremia can be approximated based on the distribution of total body water and solute and the mechanism of glucose metabolism (69-71). Hyperglycemia also promotes volume and water depletion because the osmotic diuresis is associated with water loss in excess of sodium plus potassium (72). The water deficit may average 9 liters with a sodium loss of 700 mEq (1). The thirst mechanism will be largely intact; patients with hyperglycemia are thirsty because the volume depletion will stimulate thirst. While it is usually stated that glucose is not dipsogenic (66,67,73), patients on maintenance dialysis with hyperglycemic are thirsty despite the absence of volume depletion (they generally are volume expanded) (74,75). This suggests that thirst must be due to another mechanism; whether glucose is directly dipsogenic in diabetic patients is unknown. However, a normal thirst mechanism prevents development of a hypertonic state until the patient is too weak to drink water.

Effect of Age (Figure 26). Severe hypernatremia is quite rare in adults, comprising 0.1% of hospital admissions (76), but about 10-fold common in the elderly (2). While the exact reason for this is uncertain, there are many factors that contribute to hypernatremia in elderly patients.

FIGURE 26



In the elderly, the response to plasma AVP to osmotic stimuli is increased (77), but response to volume stimulation is reduced (78). This makes AVP release one of the few things that increases with age. Thirst is also affected by age. Hypodipsia has been described in elderly patients following cerebrovascular accidents (79) even when they seem fully capable of requesting and obtaining water. Hyperdipsia has also been found in active elderly men without any other contributing factor for decreased water intake (80,81), which explains why elderly patients become dehydrated with seemingly mild stresses (fever, infection, diarrhea, diuretics or imposed water restriction prior to a medical procedure) or from hyperglycemia (81).

HYPERTONICITY: SYMPTOMS

The clinical manifestations of hypertonicity depend on solute, speed of development, and the magnitude of the increased osmolality (Figure 27). However, the most important predictor of the clinical disorder is the ability of the solute to shrink cells, primarily brain cells.

Infants with severe diarrhea or inadvertent salt poisoning are initially lethargic and listless but become quite irritable and hyperactive when stimulated. Sensorium is depressed, ranging from lethargy to coma (44,45). In adults, the sequence is similar with early lethargy, weakness, and irritability progressing to twitching, seizures, irreversible neurologic damage and death in severe cases (45,46). Since similar symptoms occur with infusion of NaCl, NaCl plus, $NaHCO_3$, sucrose, mannitol or urea (41), movement of water out of cells is thought to be responsible.

FIGURE 27

SYMPTOMS OF HYPERTONICITY

ONSET

ACUTE Lethargy, weakness, irritability
twitching, seizures, obtundation → coma, death

GRADUAL poor correlation between Na and clinical symptoms

LEVEL

SODIUM Na 148-160 31% alert
Na > 160 11% alert

GLUCOSE Posm 330-379 Lethargy
Posm > 380 coma

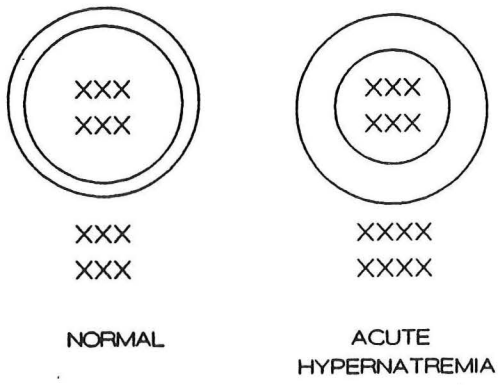
The level of hypertonicity is also important. In a study of elderly patients with hypernatremia, patients with a peak serum sodium >160 mEq/L were rarely alert (11%); although only 31% were alert with serum sodium of 148-160 (2). Depression of sensorium correlated with the degree of hypernatremia, but there was substantial scatter (2). In a study of diabetic patients without ketoacidosis, symptoms generally appeared when the plasma osmolality exceeded 330-340 mOsm/kg while coma occurred at >380 mOsm/kg (1).

In hypernatremia of more gradual onset, the symptoms and mortality rates do not always correlate with the extent of hypernatremia (2,43,82). The loss of cell volume accounts for the soft velvety sheen and doughy consistency of the skin (44). For example, patients with essential hypernatremia are alert despite modestly elevated plasma sodium. There is a report of survival in an elderly patient with Na 202 mEq/L caused by gradual dehydration occurring over several days (2). In elderly patients, the symptoms of hypernatremia are less characteristic due to the coexistence of other catastrophic medical conditions (45).

The prominence of CNS manifestations suggests that many of the signs and symptoms could be explained on a mechanical basis. The effect of acute salt loading has been extensively studied in experimental animals including kittens (43), and rabbits (41), as well as clinical observations of patients (83). Acute elevation in plasma osmolality causes subdural hemorrhages, petechial hemorrhages throughout the cortex, venous stasis and thrombotic occlusions of capillary and venous sinuses. Bleeding was usually not seen in other organs, suggesting that rigid encasement of the brain is responsible for this syndrome (Figure 28).

FIGURE 28

RESPONSE OF BRAIN TO ACUTE HYPERNATREMIA



Since the blood brain barrier is more permeable to water than electrolytes, water would move down an osmotic gradient from brain to blood with shrinkage of the brain volume. Shrinkage of the brain away from its rigid walls (41) decreases CSF pressure (39), ruptures cerebral veins, resulting in focal intracerebral and subarachnoid hemorrhages, and irreversible neurologic dysfunctions (39,83). That hemorrhages can be prevented by infusing mineral oil supports a mechanical mechanism for brain hemorrhage (39).

Brain cell response: ion accumulation. The dissociation between plasma tonicity and clinical symptoms may relate to adjustments in brain cell volume during hypertonicity. The brain does not act an ideal osmometer during acute hypernatremia, as demonstrated by Cserr in a series of elegant studies (84-87). During acute hypernatremia induced by salt loading, brain volume shrinks by 8% which is less than the 22% predicted if the brain cells acted as perfect osmometers whose internal solute content was constant (84) (Figure 29). Indeed, brain cells gain sodium, potassium and chloride in sufficient amounts to account quantitatively for tissue volume regulation. Thus, water loss and electrolyte uptake occurred simultaneously over the first 30 minutes which limited the degree of brain shrinkage (84). Subsequent quantitative analysis suggested that most of the potassium gained by brain tissue came from plasma (85) whereas the cerebral spinal fluid was the major source of sodium and chloride (86). Of interest, Battleboro rats which are unable to synthesize bioactive AVP have decreased brain sodium uptake suggesting that AVP may play a role in brain ion homeostasis (88).

FIGURE 29

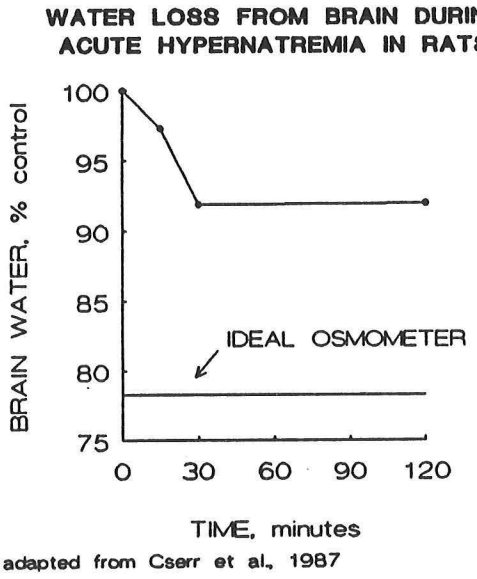
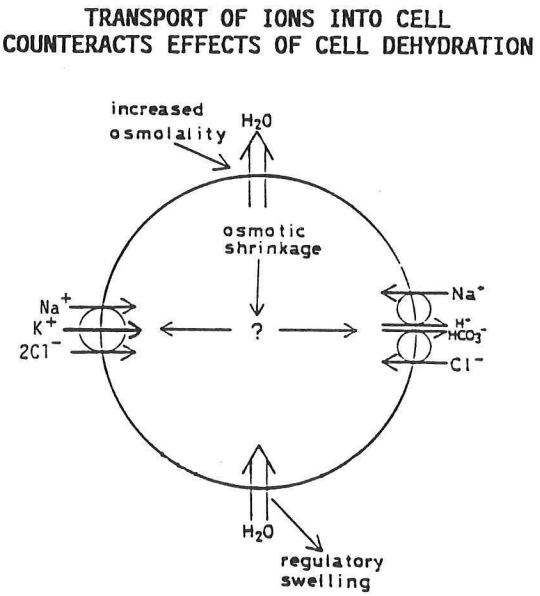


FIGURE 30



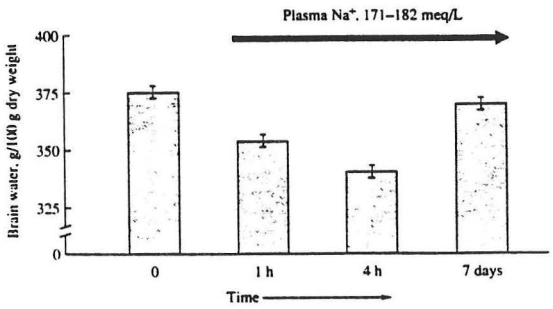
Osmotic shrinkage turns on membrane transporters which bring sodium, potassium and chloride into the cell (Figure 30). The increased cell solute content returns cell volume towards normal (89,90).

Brain cell response: accumulation of osmolytes (idiogenic osmoles). In most tissues, the ionic adjustments following hyperosmolality induced cell shrinkage do not return the cell volume back to normal. However, with prolonged hypernatremia, brain water returns to control levels (Figure 31) (91).

normal size, presumably restoring CSF pressure back to normal, and reducing the hemorrhagic complications of acute solute infusion.

FIGURE 31

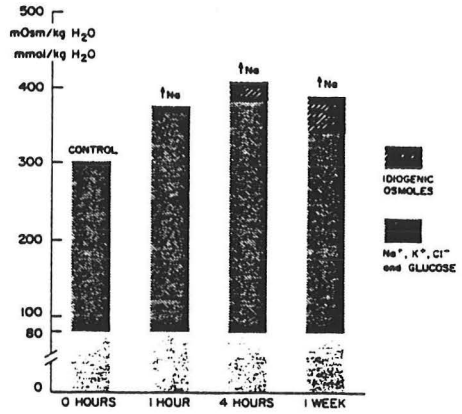
EFFECT OF HYPERNATREMIA ON
BRAIN WATER CONTENT IN RABBITS



[Ref: Arieff et al., 1977]

FIGURE 32

EFFECT OF HYPERNATREMIA ON
ON BRAIN SOLUTE CONTENT



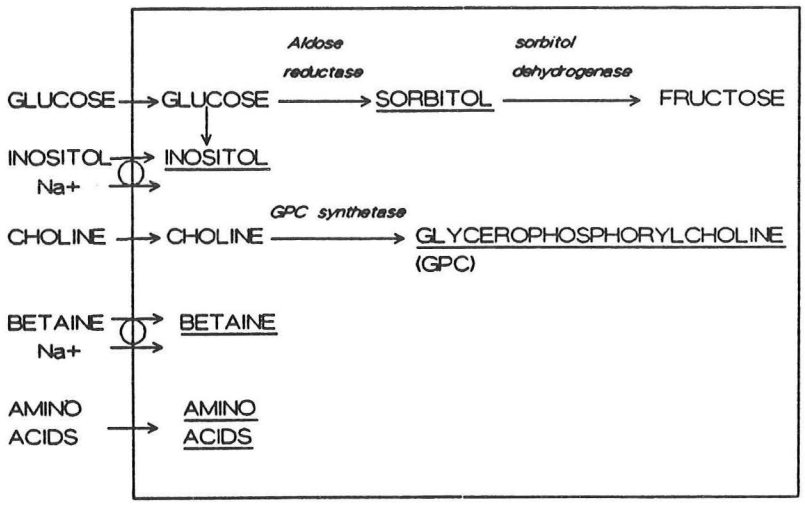
[Ref: Arieff et al., 1977]

The increase in cell volume found during sustained hypernatremia is accompanied by increases in brain solute content (Figure 32) (91), but there is a gap between the measured osmolality and the osmolality calculated from the measured solutes. These undetermined solutes were termed idiogenic osmoles by McDowell, Wolfe, and Steer (92), although Finberg was the first to suggest that idiogenic osmoles could develop in the brain during hypernatremia (43). Generation of idiogenic osmoles requires time; they are not detected after one hour of hypernatremia in rabbits, but become detectable at four hours (91).

The identity and regulatory pathways of these idiogenic osmoles have been best studied in bacteria, fungi, and the kidney where cells in the inner medulla of the kidney are subject to continual osmotic stress during periods of diuresis and antidiuresis. Certain themes have remained constant during evolution (93,94). Cells are survived in environments containing one molar urea or sodium chloride by synthesizing compounds called osmolytes which are retained inside the cell to offset the high external osmolality. Figure 33 shows a summary of the metabolic and transport pathways that regulate cell concentration of the major osmolytes. Sorbitol is produced from glucose by aldose reductase; sorbitol is degraded by sorbitol dehydrogenase (95). The other polyol, inositol, is synthesized from glucose, or enters the cell by a sodium dependent transporter (96). GPC is synthesized from choline by choline dehydrogenase (97), and betaine enters the cell via specific sodium dependent co-transporter. In addition, amino acids enter the cell via specific transporters.

FIGURE 33

REGULATION OF MAJOR OSMOLYTES



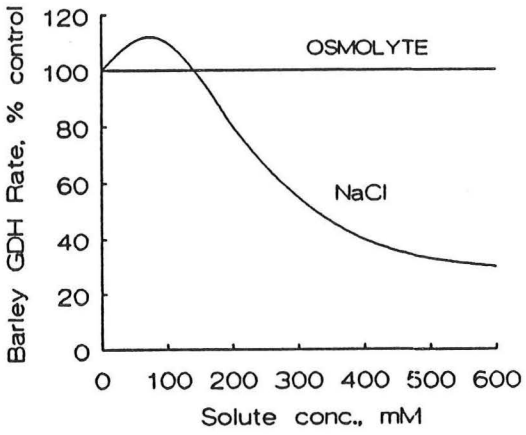
Hypernatremia increases brain amino acids (91,98-103), inositol (91,102,104-107), and GPC (102,107). Betaine increases in some studies (107), but not in others (102,108). Sorbitol (102,104) is usually absent from brain. A recent study found that brain gluatmine, gluatmate, inositol, and GPC increased during salt loading but not during water deprivation; the different results may reflect the different degrees of hypernatremia (165 vs 151 mEq/L, respectively) (102). Sites of regulation by hypertonicity, studied in cultured cells or whole animal models, include aldose reductase (109), sorbitol dehydrogenase (109), choline dehydrogenase (97), and the sodium dependent inositol (110) co-transporter as well as amino acid transporters.

As in chronic hypernatremia, cerebral dehydration in nonketotic hyperglycemia is prevented by accumulation of idiogenic osmoles (111). Maintenance of the plasma glucose at 1100 mg% for 4-6 hours causes an initial decrease in brain water content over the first 1-2 hours; however, brain water content returns to normal values by 4-6 hours. In contrast, skeletal muscle water content fall significantly after 2 hours and remains depressed (111). The increase in brain water to normal values is accompanied by increases in the accumulation of idiogenic osmoles; this process occurs in brain but not muscle (111). High glucose levels promote accumulation of sorbitol in many tissue; GPC also accumulates in cultured MDCK cells (121). The mechanism by which hyperglycemia produces depression of sensorium (see Figure 1) (1) is unknown since brain shrinkage is absent (64,112). The depression of sensorium might be caused by altered energy metabolism, or by a direct effect of hyperglycemia on the sensitivity to osmotic injury (82).

Direct Solute Effect. In addition to returning brain cell volume back to normal, osmolytes have another beneficial effect: they prevent enzyme dysfunction. Most inorganic ions and some organic anions (including arginine and urea) inhibit enzyme function at high concentrations (93,94) (Figure 34).

FIGURE 34

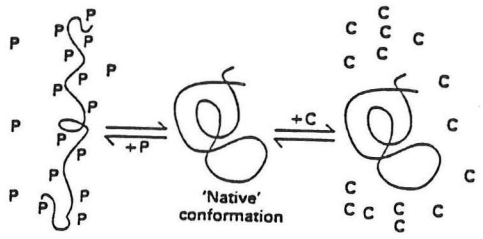
NaCl INHIBITS ENZYME FUNCTION



Redrawn from Yancey, 1982

FIGURE 35

EFFECT OF A PERTURBING (P) AND A COMPATIBLE (C) SOLUTE ON THE CONFORMATION OF A GLOBULAR PROTEIN

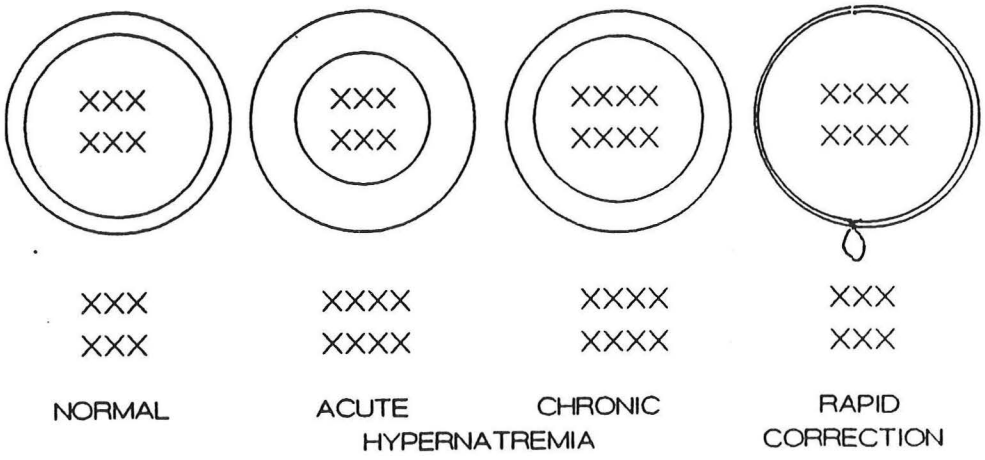


[Ref: Burg, 1988]

In contrast, high concentrations of osmolytes are nonperturbing or compatible with enzyme function (93,94,113). Perturbing solutes tend to bind macromolecules, promoting unfolding and denaturation of proteins, while compatible osmolytes are excluded from the protein surface (Figure 35) (114). Some osmolytes such as the methylamines (GPC and betaine) can counteract the effects of high urea on enzyme function and are called stabilizing osmolytes (93,94,115).

FIGURE 36

RESPONSE OF BRAIN TO HYPERNATREMIA



Consequences of Volume Regulation. Normalization of brain water content has both positive and negative consequences. First, prevention of brain shrinkage and/or replacement of perturbing solutes (Na,K,Cl) with compatible solutes (osmolytes) may explain why chronic hypernatremia is often well-tolerated even with sodiums as high as 170-200 (2,45,91,116). On the other hand, persistence of these ions and osmolytes may cause cerebral edema if the hypertonicity is rapid corrected (Figure 36) (83,91,117). Hogan et al (117) measured the water content of brain tissue and rabbits rendered chronically hypernatremic by salt loading. When the animals were rehydrated over a four hour period with 2.5% dextrose and water, 55% of the animals developed focalized or generalized seizures. The water content of the animals who had seizures with significantly greater than that of normal group of animals suggesting that the seizures could be the result of cerebral edema. Experiments in cultured brain cells indicates that osmolytes leave brain cells slowly; betaine and inositol decrease 40-70% in 1 hour, then return to control values slowly over 2-3 days in cultured glioma cells (personal communication, S. Gullans).

HYPERTONICITY: THERAPY

The therapy of a patient with hypertonicity depends upon the patient's clinical status and the specific cause of the hypertonic states. The first step is to stabilize the patient's hemodynamics, if necessary. ECF volume should be repleated with normal saline. This should restore tissue perfusion and may also lower the plasma sodium concentration since normal saline has a lower sodium concentration than that of the patient. The second step is to treat the underlying cause of hypertonicity, if possible, to prevent ongoing water loss or solute gain. Specific therapies include insulin, discontinuing the salt infusion, and taking steps to slow osmotic diuresis if present. In patients with known central diabetes insipidus, aqueous AVP can be given. The third step is to slowly correct hypernatremia, since rapid correction of hypernatremia can induce cerebral seizures, permanent neurologic damage and death (43,45,111,117). Unfortunately, the exact rate at which hypernatremia should be corrected in unknown (2). Animal studies have shown that full correction of the hypernatremia over 3-4 hours causes seizures and cerebral edema in 55% of the animals (117). Full correction of the hypernatremia in 24 hours caused cerebral edema and unexplained death in patients (45). Faster rates of correction are associated with greater mortality (2). Therefore, the current recommendation is that plasma sodium be lowered to normal gradually over 48 hours (2,112,118).

FIGURE 37

ACUTE MANAGEMENT OF HYPERNATREMIA: AMOUNT OF REPLACEMENT

Calculate approximate amount of water loss, assuming total body solute is constant:

$$TBW \cdot Na = TBW_{normal} \cdot 140$$

or (after rearranging),

$$\text{water deficit} = 0.5 \cdot BW \cdot \left(1 - \frac{140}{Na}\right)$$

The amounts of water that needs to be replaced can be approximated based on the following assumptions (Figure 37): 1) the hypernatremia is caused only by water loss without loss of total body solute and 2) the total body water is known. Since neither of these assumptions are generally true in clinical practice, this formula is at best an approximation.

In summary, the generally accepted guidelines for acute management of patients with hypernatremia are to replace half the deficit over 12-24 hours. In elderly patients, half the deficit should be replaced over 24 hours. The suggested rate of decrease of plasma Na ranges from 0.5 mEq/hr (119) in chronic hypernatremia to 2 mEq/hr (59) in acute hypernatremia, but most suggest $\leq$ 1 mEq/hr (112). A 24 year old women survived without subsequent neurological damage after her severe iatrogenic hypernatremia (Na 178) was corrected at a rate of 3.6 mEq/hr (59). This fast a rate cannot be recommended. Because the water deficit formula is only an approximation, serial measurements of plasma sodium are required to ensure that the actual rate of correction is attained. The remaining deficit is then replaced over the second 24 hour period. The oral route should be used if possible because intravenous administration of large amounts of D5W can cause marked hyperglycemia if glucose is given faster than the patient can metabolize it (120). Salt excess can be treated with furosemide (to remove excess salt), and water; plasma Na may drop rapidly (59,62).

REFERENCES

1. Arieff, A.I., and H.J. Carroll. 1974. Cerebral edema and depression of sensorium in nonketotic hyperosmolar coma. Diabetes 23:525-531.
2. Snyder, N.A., D.W. Feigal, and A.I. Arieff. 1987. Hypernatremia in elderly patients. A heterogeneous, morbid, and iatrogenic entity. Ann. Intern. Med. 107:309-319.
3. Zimmerman, E.A., L.-Y. Ma, and G. Nilaver. 1987. Anatomical basis of thirst and vasopressin secretion. Kidney Int. 32:S14-S19.
4. Schmale, H., S. Fehr, and D. Richter. 1987. Vasopressin biosynthesis-from gene to peptide hormone. Kidney Int. 21:S8-S13.
5. Thrasher, T.N. 1982. Osmoreceptor mediation of thirst and vasopressin secretion in the dog. Fed. Proc. 41:2528-2532.
6. Baylis, P.H., and C.J. Thompson. 1988. Osmoregulation of vasopressin secretion and thirst in health and disease. Clin. Endocrinol. 29:549-576.
7. Robertson, G.L., P. Aycinena, and R.L. Zerbe. 1982. Neurogenic disorders of osmoregulation. Am. J. Med. 72:339-353.
8. Verney, E.B. 1947. The antidiuretic hormone and factors which determine its release. Proc. Royal Soc. Lond. B. 135:25-106.
9. Dunn, F.L., T.J. Brennan, A.E. Nelson, and G.L. Robertson. 1973. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J. Clin. Invest. 52:3212-3219.
10. Salata, R.A., J.G. Verbalis, and A.G. Robinson. 1987. Cold water stimulation of oropharyngeal receptors in man inhibits release of vasopressin. J. Clin. Endocrinol. Metab. 65:561-567.
11. Thompson, C.J., J.M. Burd, and P.H. Baylis. 1987. Acute suppression of plasma vasopressin and thirst after drinking in hypernatremic humans. Am. J. Physiol. 252:R1138-R1142.
12. Thompson, C.J., and P.H. Baylis. 1988. Osmoregulation of thirst. J. Endocri. 117:155-157.
13. Zimmerhackl, B.L., C.R. Robertson, and R.L. Jamison. 1987. The medullary microcirculation. Kidney Int. 31:641-647.
14. Grantham, J.J., and M.B. Burg. 1966. Effect of vasopressin and cyclic AMP on permeability of isolated collecting tubules. Am. J. Physiol. 211:255-259.
15. Knepper, M.A., and F. Roch-Ramel. 1987. Pathways of urea transport in the mammalian kidney. Kidney Int. 31:629-633.
16. Sands, J.M., H. Nonoguchi, and M.A. Knepper. 1987. Vasopressin effects on urea and H_2O transport in inner medullary collecting duct subsegments. Am. J. Physiol. 253:F823-F832. 17. Star, R.A., H. Nonoguchi, R. Balaban, and M.A. Knepper. 1988. Calcium and cyclic adenosine monophosphate as second messengers for vasopressin in the rat inner medullary collecting duct. J. Clin. Invest. 81:1879-1888.
18. Knepper, M.A., J.M. Sands, H. Nonoguchi, R.A. Star, and R.K. Packer. 1988. Inner medullary collecting duct. In Nephrology. A.M. Davison, editor. TransMedica Europe Limited, Bailliere Tindall. 317-331.

19. Star, R.A. 1990. Role of apical and basolateral membranes in transcellular urea transport across the rat inner medullary collecting duct cell. Kidney Int. 37;590. (Abstract)
20. Strange, K., and K.R. Spring. 1987. Cell membrane water permeability of rabbit cortical collecting duct. J. Membr. Biol. 96:27-43.
21. Ausiello, D.A., K.L. Skorecki, A.S. Verkman, and J.V. Bonventre. 1987. Vasopressin signaling in kidney cells. Kidney Int. 31:521-529.
22. Brown, D., and L. Orci. 1983. Vasopressin stimulates formation of coated pits in rat kidney collecting ducts. Nature 302:253-255.
23. Brown, D., G.I. Shields, H. Valtin, J.F. Morris, and L. Orci. 1985. Lack of intramembranous particle clusters in collecting ducts of mice with nephrogenic diabetes insipidus. Am. J. Physiol. 249:F582-F589.
24. Verkman, A.S., W.I. Lencer, D. Brown, and D.A. Ausiello. 1988. Endosomes from kidney collecting tubule cells contain the vasopressin-sensitive water channel. Nature 333:268-269.
25. Verkman, A.S., P. Weyer, D. Brown, and D.A. Ausiello. 1989. Functional water channels are present in clathrin-coated vesicles from bovine kidney but not from brain. J. Biol. Chem. 264:20608-20613.
26. Ausiello, D. 1989. Cellular biology of the water channel. Kidney Int. 36:497-506.
27. Andersson, B. 1952. Polydipsia caused by intrahypothalamic injections of hypertonic NaCl solutions. Experimentia 8:157.
28. Hammond, D.N., G.W. Moll, G.L. Robertson, and E. Chelmicka-Schorr. 1986. Hypodipsic hypernatremia with normal osmoregulation of vasopressin. N. Engl. J. Med. 315:433-436.
29. Robertson, G.L., and T. Berl. 1986. Water Metabolism. In The Kidney. B.M. Brenner, and F.C. Rector,Jr., editors. W.B. Saunders, Philadelphia. 385-432.
30. Robertson, G.L. 1984. Abnormalities of thirst regulation. Kidney Int. 25:460-469.
31. Thompson, C.J., J. Bland, J. Burd, and P.H. Baylis. 1986. The osmotic thresholds for thirst and vasopressin release are similar in healthy man. Clin. Sci. 71:651-656.
32. Wolf, A.V. 1950. Osmometric analysis of thirst in man and dog. J. Clin. Invest. 161:75-86. 33. Adolph, E.F. 1950. Thirst and its inhibition in the stomach. J. Clin. Invest. 161:374-386. 34. Adolph, E.F. 1982. Termination of drinking: satiation. Federation Proceedings 41:2533-2535.
35. Greenleaf, J.E., and M.J. Fregly. 1982. Dehydration-induced drinking: peripheral and central aspects. Federation Proceedings 41:2507-2507.
36. Phillips, M.I., W.E. Hoffman, and S.L. Bealer. 1982. Dehydration and fluid balance: central effects of angiotensin. Fed. Proc. 41:2520-2527.
37. Mann, J.F.E., A.K. Johnson, D. Ganten, and E. Ritz. 1987. Thirst and the renin-angiotensin system. Kidney Int. 21:S27-S34.
38. Zerbe, R.L., and G.L. Robertson. 1987. Osmotic and nonosmotic regulation of thirst and vasopressin secretion. In Clinical Disorders of Fluids and Electrolyte Metabolism. M.H. Maxwell, C.R. Kleeman, and R.G. Narins, editors. McGraw-Hill, NY. 61-78.
39. Luttrell, C.N., L. Finberg, and L.P. Drawdy. 1959. Hemorrhagic encephalopathy induced by hypernatremia. Arch. Neurol. 1:153-160.

40. Kleeman, C.R., H. Davson, and E. Levin. 1962. Urea transport in the central nervous system. Am. J. Physiol. 203:739-747.
41. Sotos, J.F, P.R. Dodge, P. Meara, and N.B. Talbot. 1960. Studies in experimental hypertonicity: Pathogenesis of the clinical syndrome, biochemical abnormalities, and cause of death. Pediatrics 26:925-938.
42. Cserr, H.F., J.D. Fenstermacher, and D.P. Rall. 1978. Comparative aspects of brain barrier systems for nonelectrolytes. Am. J Physiol. 234:R52-R60.
43. Finberg, L., C. Luttrell, and H. Redd. 1959. Pathogenesis of lesions in the nervous system in hypernatremic states. II. Experimental studies of gross anatomic changes and alterations of chemical composition of the tissues. Pediatrics 23:46-53.
44. Finberg, L. 1959. Pathogenesis of lesions in the nervous system in hypernatremic states. I. Clinical Observations of infants. Pediatrics 40-45.
45. Arieff, A.I., and R. Guisado. 1976. Effects on the central nervous system of hypernatremic and hyponatremic states. Kidney Int. 10:104-116.
46. Ross, E.J., and S.B. Christie. 1969. Hypernatremia. Medicine (Baltimore.) 48:441-473.
47. Ganguly, A., and G.L. Robertson. 1980. Elevated threshold for vasopressin release in primary aldosteronism. Clin. Res. 28:330A.(Abstract)
48. Avioli, L.V., L.E. Earley, and H.K. Kashima. 1962. Chronic and sustained hypernatremia, absence of thirst, diabetes insipidus, and adrenocorticotrophin insufficiency resulting from widespread destruction of the hypothalamus. Ann. Intern. Med. 56:131-140.
49. Halter, J.B., A.P. Goldberg, G.L. Robertson, and D. Porte,Jr.. 1977. Selective osmoreceptor dysfunction in the syndrome of chronic hypernatremia. J. Clin. Endocrinol. Metab. 44:609-616.
50. Thompson, C.J., J. Freeman, C.O. Record, and P.H. Baylis. 1987. Hypernatremia due to a reset osmostat for vasopressin release and thirst, complicated by nephrogenic diabetes insipidus. Postgraduate Medical J. 63:979-982.
51. Yamamoto, T., M. Shimizu, J. Fukuyama, and T. Yamaji. 1988. Pathogenesis of extracellular fluid abnormalities of hypothalamic hypodipsia-hypernatremia syndrome. Endocrinol. Jpn. 35:915-924.
52. DeRubertis, F.R., M.F. Michelis, and B.B. Davis. 1974. "Essential" hypernatremia. Report of three cases and review of the literature. Arch. Intern. Med. 134:889-895.
53. Perez, G.O., J.R. Oster, and G.L. Robertson. 1989. Severe hypernatremia with impaired thirst. Am. J. Nephrol. 9:421-434.
54. Lindheimer, M.D., W.M. Barron, and J.M. Davison. 1989. Osmoregulation of thirst and vasopressin release in pregnancy. Am. J. Physiol. 257:F159-F169.
55. Valtin, H., and B.R. Edwards. 1987. GFR and the concentration of urine in the absence of vasopressin. Berliner-Davidson re-explored. Kidney Int. 31:634-640.
56. De Wardener, H.E., and A. Herxheimer. 1957. The effect of a high water intake on the kidney's ability to concentrate the urine in man. J. Physiol. (Lond) 139:42-52.
57. Zerbe, R.L., and G.L. Robertson. 1981. A comparison of plasma vasopressin measurements with a standard indirect test in the differential diagnosis of polyuria. N. Engl. J. Med. 305:1539-1546.

58. Earley, L.E., and J. Orloff. 1962. The mechanism of antidiuresis associate with the administration of hydrochlorothiazide to patients with vasopressin-resistant diabetes insipidus. J. Clin. Invest. 41:1988-1997.
59. Elisaf, M., H. Litou, and K.C. Siamopoulos. 1989. Survival after severe iatrogenic hypernatremia. Am. J. Kidney Dis. 14:23-231.
60. Cassorla, F.G., J.R. Gill, P.W. Gold, and S.W. Rosen. 1985. Nosocomial hypernatremia. N. Engl. J. Med. 313:329-329.
61. Finberg, L. 1973. Hypernatremic (hypertonic) dehydration in infants. N. Engl. J. Med. 289:196-198.
62. Fujiwara, P., M. Berry, P. Hauger, and M. Cogan. 1985. Chicken-soup hypernatremia. N. Engl. J. Med. 313:1161-1162.
63. Addleman, M., A. Pollard, and R.F. Grossman. 1985. Survival after severe hypernatremia due to salt ingestion by an adult. Am. J. Med. 78:176-178.
64. Arieff, A.I., and H.J. Carroll. 1972. Nonketotic hyperosmolar coma with hyperglycemia: clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. Medicine (Baltimore.) 51:73-94.
65. Thompson, C.J., S.N. Davis, and P.H. Baylis. 1989. Effect of blood glucose concentration on osmoregulation in diabetes mellitus. Am. J. Physiol. 256:R597-R604.
66. Thompson, C.J., S.N. Davis, P.C. Butler, J.A. Charlton, and P.H. Baylis. 1989. Osmoregulation of thirst and vasopressin secretion in insulin-dependent diabetes mellitus. Clin. Sci. 74:599-606.
67. Zerbe, R.L., and G.L. Robertson. 1983. Osmoregulation of thirst and vasopressin secretion in human subjects: effect of various solutes. Am. J. Physiol. 244:E607-E614.
68. Robertson, G.L. 1987. Physiology of ADH secretion. Kidney Int. 32:S-20-S-26.
69. Roscoe, J.M., M.L. Halperin, F.S. Rolleston, and M.B. Goldstein. 1975. Hyperglycemia-induced hyponatremia: metabolic considerations in calculation of serum sodium depression. Can. Med. Assoc. J. 112:452-453.
70. Katz, M.A. 1973. Hyperglycemia-induced hyponatremia - calculation of expected serum sodium depression. N. Engl. J. Med. 289:843-844.
71. Moran, S.M., and R.L. Jamison. 1985. The variable hyponatremic response to hyperglycemia. West. J. Med. 142:49-53.
72. Rose, B.D. 1986. New approach to disturbances in the plasma sodium concentration. Am. J. Med. 81:1033-1040.
73. Fitzsimons, J.T. 1961. Drinking by nephrectomized rats injected with various substances. J. Physiol. (Lond) 155:563-579.
74. Tzamaloukas, A.H., A.R. Levinstone, and K.D. Gardner. 1982. Hyperglycemia in advanced renal failure: sodium and water metabolism. Nephron 31:40-44.
75. Tzamaloukas, A.H., and P.S. Avasthi. 1986. Effect of hyperglycemia on serum sodium concentration and tonicity in outpatients on chronic dialysis. Am. J. Kidney Dis. 7:477-482.
76. Daggett, P., J. Deanfield, F. Moss, and D. Reynolds. 1979. Severe hypernatremia in adults. Brit. Med. J. 1:11777-11180.

77. Helderman, J.H., R.E. Vestal, J.W. Rowe, J.D. Tobin, R. Andres, and G.L. Robertson. 1978. The response of arginine vasopressin to intravenous alcohol and hypertonic saline in man: the impact of aging. J. Gerontol. 33:39-47.
78. Rowe, J.W., K.L. Minaker, D. Sparrow, and G.L. Robertson. 1982. Age-related failure of volume-pressure-mediated vasopressin release. J. Clin. Endocrinol. Metab. 54:661-664.
79. Miller, P.D., R.A. Krebs, B.J. Neal, and D.O. McIntyre. 1982. Hypodipsia in geriatric patients. Am. J. Med. 73:354-356.
80. Phillips, P.A., D. Phil, B.J. Rolls, J.G.G. Ledingham, M.L. Forsling, J.J. Morton, M.J. Crowe, and L. Wollner. 1984. Reduced thirst after water deprivation in healthy elderly men. N. Engl. J. Med. 311:753-759.
81. Leaf, A. 1984. Dehydration in the elderly. N. Engl. J. Med. 311:791-792.
82. Pollock, A.S., and A.I. Arieff. 1980. Abnormalities of cell volume regulation and their function consequences. Am. J. Physiol. 239:F195-F205.
83. Morris-Jones, P.H., I.B. Houston, and R.C. Evans. 1967. Prognosis of the neurological complications of acute hypernatremia. The Lancet December:1385-1389.
84. Cserr, H.F., M. DePasquale, and C.S. Patlak. 1987. Regulation of brain water and electrolytes during acute hyperosmolality in rats. Am. J. Physiol. 253:F522-F529.
85. Cserr, H.F., M. DePasquale, and C.S. Patlak. 1987. Volume regulatory influx of electrolytes from plasma to brain during acute hyperosmolality. Am. J. Physiol. 253:F530-F537.
86. Pullen, R.G.L., M. DePasquale, and H.F. Cserr. 1987. Bulk flow of cerebrospinal fluid into brain in response to acute hyperosmolality. Am. J. Physiol. 253:F538-F545.
87. Cserr, H.F. 1989. Role of secretion and bulk flow of brain interstitial fluid in brain volume regulation. Ann. N. Y. Acad. Sci. 9-20.
88. DePasquale, M., C.S. Patlak, and H.F. Cserr. 1989. Brain ion and volume regulation during acute hypernatremia in Brattleboro rats. Am. J. Physiol. 256:F1059-F1066.
89. Ballanyi, K., and P. Grafe. 1988. Cell volume regulation in the nervous system. Renal Physiol. Biochem. 11:142-157.
90. Chamberlin, M.E., and K. Strange. 1989. Anisosmotic cell volume regulation: A comparative view. Am. J. Physiol. 257:C159-C173.
91. Arieff, A.I., R. Guisado, and V.C. Lazarowitz. 1977. Pathophysiology of hyperosmolar states. In Disturbances in Body Fluid Osmolality. T.E. Andreoli, J.J. Grantham, and F.C. Rector,Jr., editors. American Physiological Society, Bethesda. 227-250.
92. McDowell, M.E., A.V. Wolf, and A. Steer. 1955. Osmotic volumes of distribution. Idiogenic changes in osmotic pressure associated with administration of hypertonic solutions. Am. J. Physiol. 180:545-558.
93. Yancey, P.H., M.E. Clark, S.C. Hand, R.D. Bowlus, and G.N. Somero. 1982. Living with water stress: evolution of osmolyte systems. Science 217:1214-1222.
94. Yancey, P.H., and M.B. Burg. 1989. Distribution of major organic osmolytes in rabbit kidneys in diuresis and antidiuresis. Am. J. Physiol. 257:F602-F607.
95. Moriyama, T., A. Garcia-Perez, and M.B. Burg. 1989. Osmotic regulation of aldose reductase protein synthesis in renal medullary cells. J. Biol. Chem. 264:16810-16814.

96. Nakanishi, T., and M.B. Burg. 1989. Osmoregulatory fluxes of myo-inositol and betaine in renal cells. Am. J. Physiol. 257:C964-C970.
97. Grossman, E.B., and S.C. Hebert. 1989. Renal inner medullary choline dehydrogenase activity: characterization and modulation. Am. J Physiol. 256:F107-F112.
98. Chan, P.H., and R.A. Fishman. 1979. Elevation of rat brain amino acids, ammonia and idiogenic osmoles induced by hyperosmolality. Brain Research 161:293-301.
99. Lockwood, A.H. 1980. Adaptation to hyperosmolality in the rat. Brain Res. 200:216-219.
100. Trachtman, H., R. Barbour, J.A. Sturman, and L. Finberg. 1988. Taurine and osmoregulation: taurine is a cerebral osmoprotective molecule in chronic hypernatremic dehydration. Pediatr. Res. 23:35-39.
101. Thurston, J.H., R.E. Hauhart, and J.A. Dirgo. 1980. Taurine: A role in osmotic regulation of mammalian brain and possible clinical significance. Life Sciences 26:1561-1568.
102. Heilig, C.W., M.E. Stromski, J.D. Blumenfeld, J.P. Lee, and S.R. Gullans. 1989. Characterization of the major brain osmolytes that accumulate in salt-loaded rats. Am. J. Physiol. 257:F1108-F1116.
103. Arieff, A.I., C.R. Kleeman, A. Keushkerian, and H. Bagdoyan. 1972. Brain tissue osmolality: Method of determination and variations in hyper- and hypo-osmolar states. J. Lab. Clin. Med. 79:334-343.
104. Lohr, J.W., J. McReynolds, T. Grimaldi, and M. Acara. 1988. Effect of acute and chronic hypernatremia on myoinositol and sorbitol concentration in rat brain and kidney. Life. Sci. 43:271-276.
105. Darrow, D.C., and H. Yannet. 1935. The changes in the distribution of body water accompanying increase and decrease in extracellular electrolyte. J. Clin. Invest. 14:266-275.
106. Morrison, R., K. Strange, C. Heilig, and S. Gullans. 1990. Hypertonicity-induced inositol accumulation in C6 glioma cells: A model of brain osmoregulation. Kidney Int. 37:586.(Abstract)
107. Lien, Y.H., J.I. Shapiro, and L. Chan. 1990. Characterization of brain idiogenic osmoles accumulated in uremia and hypernatremia. Kidney Int. 37:538.(Abstract)
108. Gullans, S.R., C.W. Heilig, M.E. Stromski, and J.D. Blumenfeld. 1989. Methylamines and polyols in kidney, urinary bladder, urine, liver, brain, and plasma. An analysis using ^{1}H nuclear magnetic resonance spectroscopy. Renal Physiol. Biochem. 12:191-201.
109. Sands, J.M., and D.C. Schrader. 1990. Aldose reductase and sorbitol dehydrogenase activities vary with hydration in microdissected rat inner medullary collecting duct segments. Kidney Int. 37:588.(Abstract)
110. Nakanishi, T., R.J. Turner, and M.B. Burg. 1989. Osmoregulatory changes in myo-inositol transport by renal cells. Proc. Natl. Acad. Sci. USA 86:6002-6006.
111. Arieff, A.I., and C.R. Kleeman. 1973. Studies on mechanisms of cerebral edema in diabetic comas. Effects of hyperglycemia and rapid lowering of plasma glucose in normal rabbits. J. Clin. Invest. 52:571-583.

112. Arieff, A.I. 1985. Effects of water, acid-base, and electrolytes disorders on the central nervous system. In Fluid Electrolyte and Acid-Base Disorders. A.I. Arieff, and R.A. DeFronzo, editors. Churchill Livingston, NY. 969-1040.
113. Somero, G.N. 1986. Protons, osmolytes, and fitness of internal milieu for protein function. Am. J. Physiol. 251:R197-R213.
114. Burg, M.B. 1988. Role of aldose reductase and sorbitol in maintaining the medullary intracellular milieu. Kidney Int. 33:635-641.
115. Moriyama, T., A. Garcia-Perez, and M.B. Burg. 1990. High urea induces accumulation of different organic osmolytes than does high NaCl in renal medullary cells. Kidney Int. 37:586.(Abstract)
116. Holliday, M.A., MN. Kalayci, and J. Harrah. 1968. Factors that limit brain volume changes in response to acute and sustained hyper- and hyponatremia. J. Clin. Invest. 47:1916-1928.
117. Hogan, G.R., P.R. Dodge, S.R. Gill, S. Master, and J.F. Sotos. 1969. Pathogenesis of seizures occurring during restoration of plasma tonicity to normal in animals previously chronically hypernatremic. Pediatrics 43:54-64.
118. Rose, B.D. 1989. Hyperosmolal states - hypernatremia. In Clinical Physiology of Acid-Base and Electrolyte Disorders. B.D. Rose, editor. McGraw-Hill , New York. 639-675.
119. Kleeman, C.R. 1989. Metabolic coma. Kidney Int. 36:1142-1158.
120. Marsden, P.A., and M.L. Halperin. 1985. Pathophysiological approach to patients presenting with hypernatremia. Am. J. Nephrol. 5:229-235.
121. Heilig, D.W., B. Thorens, R. Chaillet, A. Yu, S. DiPietro, B.M. Brenner, and S.R. Gullens. 1990. Role of glucose in glycerophosphorylcholine accumulation by MDCK cells. Kidney Int. 37: 582. (Abstract).