Neurol.

DISORDERS OF THIRST

MEDICAL GRAND ROUNDS

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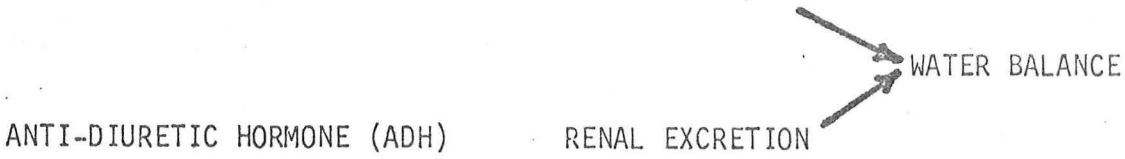
INTRODUCTION

Water balance in man is achieved by closely attuned and interrelated mechanisms that regulate intake and output (Figure 1). In normal man, water intake is regulated by drinking while



water output is regulated by renal excretion. Drinking is a complex function controlled by mechanisms that will be described below. Renal excretion of water in normal man is under the hormonal control of antidiuretic hormone (ADH). A derangement in water balance may develop due to abnormalities in either the intake limb, the excretion limb, or both areas simultaneously. The discussion today will involve the disorders that occur primarily in the intake limb of water balance, that is, in disorders of thirst. Since the areas in the central nervous system that control thirst and ADH release are closely related, many disorders of thirst are also associated with disorders of ADH release. Thus, the physiology of normal ADH release must be understood to fully understand disorders of thirst.

Thirst is a sensation that is important for our survival but one that we experience infrequently. Thirst is basically an emergency mechanism which functions to repair an actual deficit of water. Thirst, or need-induced drinking, has also been called primary drinking (1). In day to day living, our need for water is usually satisfied by habitual and anticipated drinking; this type of drinking has been called secondary. When food and water are freely available and climatic conditions are not extreme, thirst is rarely experienced. When these normal patterns of drinking do not satisfy our daily need for water, or when we are subjected to the stress of dehydration, thirst is experienced and drives us to seek water. A typical diet normally provides about 1 liter of water per day and another liter is usually added from the drinking that accompanies eating or social activities. Thus, non-thirst motivated drinking is usually sufficient to replace the normal obligatory losses of water that occur from skin, lungs, and kidneys. When water losses exceed customary daily water intake, thirst is activated to prevent serious dehydration. Thus, thirst, or primary

drinking, is essentially a safeguard mechanism. Secondary drinking is not induced by an existing need for water as it is in primary drinking. Mechanisms behind secondary drinking are unknown but it appears to depend on oropharyngeal cues which have the characteristics of an autonomous circadian rhythm (1).

Osmotic stimulation of thirst and ADH release. The physiologic deviations from normal water balance that stimulate thirst also stimulate the release of antidiuretic hormone from the posterior pituitary. However, while antidiuretic hormone secretion and water intake are regulated by the same mechanisms, there is a lower stimulus threshold for ADH release than for activation of thirst. This relationship is illustrated in Figure 2.

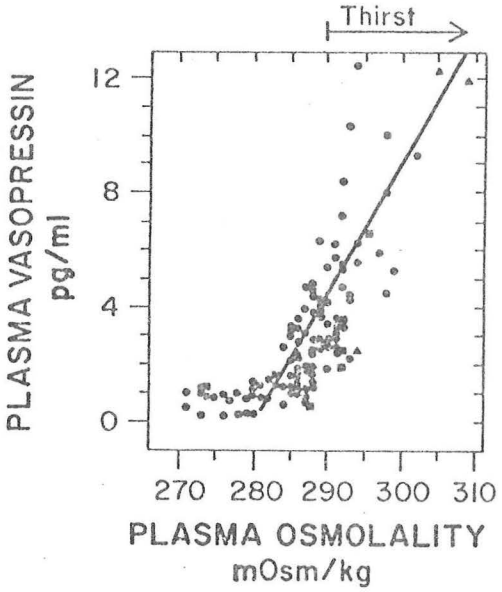


Fig. 2 Thirst and antidiuretic function in healthy adults (2).

This study, performed in normal adults deprived of water, shows that a rising plasma osmolality stimulates ADH (vasopressin) release prior to the development of thirst. The benefit of a system in which the osmotic set point for ADH release and thirst are different is that under normal conditions water balance can be maintained within narrow limits solely as a result of secondary or non-thirst mediated drinking. The alternative system in which both set points are the same would subject the individual to the demands of thirst numerous times during an average day.

Several additional relationships can be seen in Figure 2. At a plasma omolality below 280 mOsmol/kg, plasma ADH is suppressed to undetectable levels. At plasma osmolalities above 280 mOsm/kg, ADH secretion rises in direct proportion to the strength of the osmotic stimulus. The sensitivity of this system is such that a 1% rise in plasma osmolality is sufficient to stimulate a detectable increase in plasma ADH. As is clear in Figure 3, maximum urinary osmolality of approximately

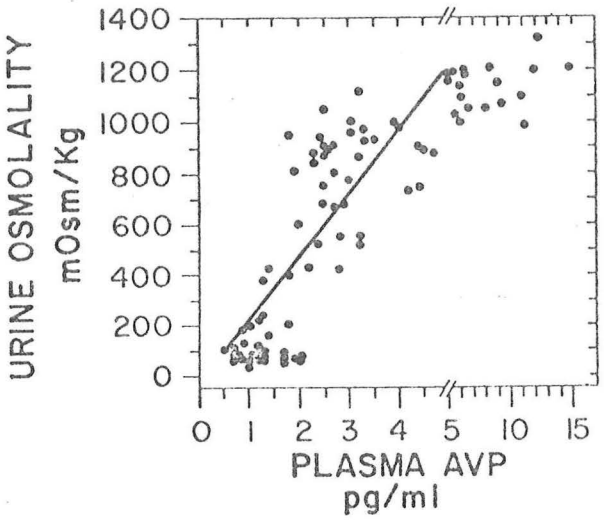
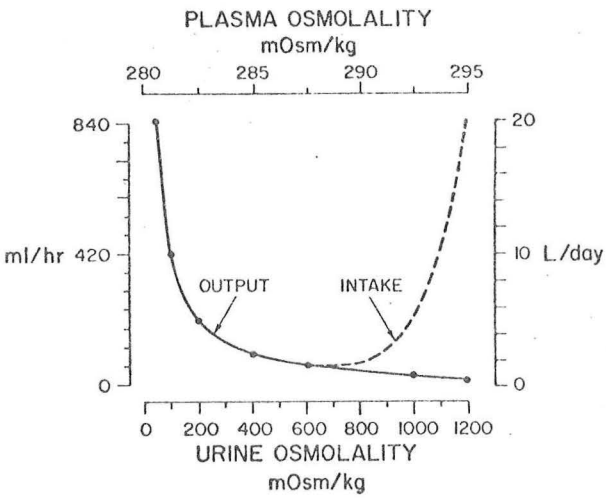


Fig. 3 Urine osmolality as function of plasma AVP (2).

1200 mOsmol/kg is achieved at plasma vasopressin level of 5 pg/ml. Since ADH has its affect only on the water excretion limb of water balance, by itself it cannot prevent hypertonic dehydration, it can only slow its development. Under normal conditions this is all that is required, since secondary drinking provides sufficient water each day to prevent dehydration. The interplay between secondary drinking and ADH release is sufficient to maintain plasma osmolality at an average value of 287 mOsm/kg H_2O (2). Adult humans are not usually aware of a thirst stimulus until plasma osmolality rises to 290 mOsmol/kg (2). This is about the level at which antidiuretic hormone concentrations are sufficient to produce a maximum antidiuresis. Above this 290 mOsmol/kg threshold the thirst stimulus increases proportionately and becomes very intense at osmolality levels above 300 mOsmol/kg. Figure 4 reveals the quantitative affects of intake and output at

Fig. 4 Relationship between plasma osmolality and water intake or output in healthy adults (2).



different levels of plasma osmolality (2) . For adult humans under normal circumstances, total intake and output of water come into balance at a plasma osmolality about halfway between the osmotic threshold for thirst and ADH release, i.e. approximately 287 mOsmol/kg. If plasma osmolality falls from this set point, ADH levels fall, urinary osmolality falls, and water output increases. If plasma osmolality increases above 287 mOsmol/kg, ADH release increases and thirst is stimulated. It is further clear from Figure 4 that the body defends a plasma osmolality of approximately 287 mOsmol/kg vigorously since a water intake of as much as 20 liters per day will not cause hypotonicity of body fluids, since ADH will be maximally suppressed and the kidneys will excrete all of the water. Conversely, in the total absence of ADH such as occurs in diabetes insipidus, hypertonicity will not occur provided that the thirst mechanism is working properly and water is readily available. Thus, disorders of body tonicity will not occur unless there are abnormalities or disorders that interfere with the full expression of the thirst and ADH threshold barriers.

There are two main regulatory signals in primary or need-induced drinking one arising from the cellular compartment and the other arising from the extracellular compartment. Cellular dehydration is generally considered to be the most sensitive stimulus for thirst and ADH release and this type of regulation has been designated osmotic. Cellular dehydration probably accounts for drinking in the following circumstances; 1) water deprivation, 2) infusion of hypertonic solutions of solutes that do not penetrate into cells, and 3) potassium depletion. The osmosensitive neurons are located in the hypothalmus near to but separate from the cell bodies of the neurohypophysis (Figure 5). By mechanisms that are not clearly understood, these

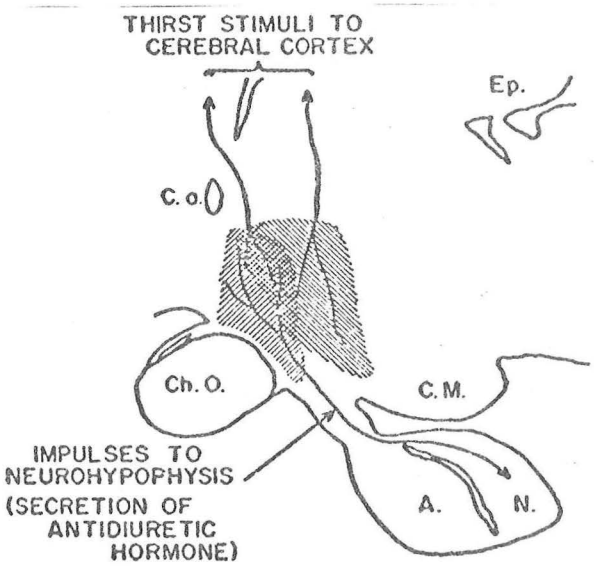


Fig. 5 Anatomy of hypothalamic osmoreceptors for thirst (hatched area to right) and antidiuresis (hatched area to the left).

osmoreceptor neurons are able to detect small changes in the concentration of plasma sodium and other solutes and convert

this information into a nervous signal that influences both thirst and ADH secretion. Verney (3) originally suggested that the osmoreceptor cells were excited primarily by a diminution of their own volume. Robertson et al (4) have confirmed that ADH release probably occurs as a result of changes in cell volume. Figure 6 demonstrates that hypertonic saline and hypertonic

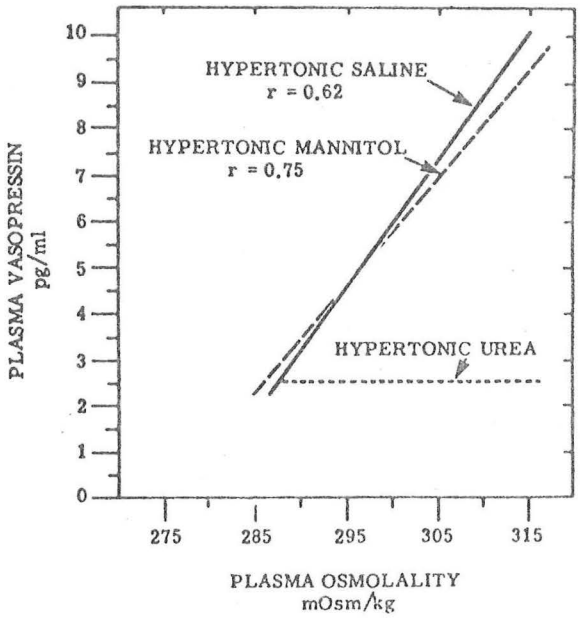


Fig. 6 Effect of hypertonic solutions of saline, mannitol and urea on plasma vasopressin levels (4).

mannitol, molecules restricted to the extracellular compartment, raise plasma osmolality and stimulate the release of ADH. In contrast, hypertonic urea, a molecule that moves freely across all membranes, raises plasma osmolality, but does not stimulate ADH release. Anderson (5) has proposed an alternative theory. He has suggested that receptors in the region of the third cerebral ventricle are sensitive to the concentration of sodium in cerebrospinal fluid and are responsible for stimulating the responses to cellular dehydration. On balance, the cell volume theory still seems to be the best substantiated of the two (6).

Non-osmotic stimuli of thirst and ADH release. Under usual circumstances the release of ADH and the stimulation of thirst are under the control of osmotic factors. However, extracellular deficits of water may stimulate thirst via stretch receptors in the capacitance vessels in the thorax. Thus, extracellular dehydration leads to drinking after 1) hemorrhage, 2) sodium depletion, 3) vomiting, and 4) diarrhea. While dehydration of either the intracellular or extracellular compartment will stimulate thirst, dehydration of the intracellular compartment represents the most sensitive controlling factor. The physiological responses to reduced extracellular fluid volume are depicted in Figure 7, and

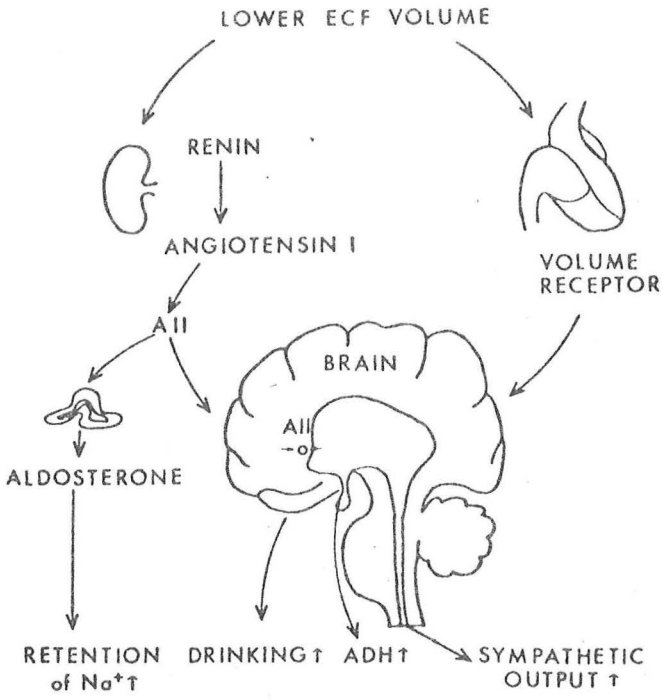
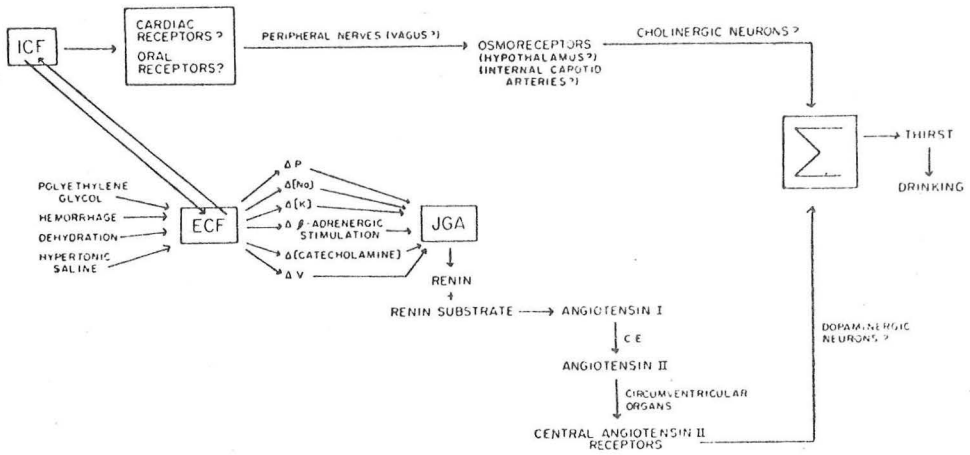


Fig. 7 Physiological response to reduced extracellular volume (7).

indicate that thirst and ADH release in this situation occur via two pathways (7). Volume receptors in the low pressure side of the heart detect changes and relay this information to the brain thereby inducing water replacement and retention actions such as thirst and vasopressin release. In addition, angiotensin is formed as a result of renin release secondary to lowered renal blood pressure and blood flow. Thus, there are at least 3 stimuli for thirst; osmotic, angiotensin II, and volume receptor stimulation (hypovolemia). These stimuli may act singly or in unison. During water deprivation both the extracellular and intracellular compartments lose water which causes a signaling of thirst to the brain by all 3 stimuli. Angiotensin II is a very potent dipsogen that induces animals to drink at low dose levels, particularly if injected directly into the brain (1). However, the dose required to produce thirst by IV infusion is orders of magnitude higher than that required by the intraventricular brain route. The exact quantitative relationship between the degree of water deprivation and the amount of angiotensin generated peripherally and whether that amount is sufficient to induce thirst centrally has not been established. However, it is indisputable that when animals are dehydrated their angiotensin levels rise and the animals are thirsty. It is also clear that angiotensin in very low doses (less than 10^{-15} M) exerts powerful dipsogen effects when injected into the brain and that there are angiotensin receptors in the brain (7). If angiotensin in the blood does cause natural thirst, it still remains to be explained how it enters the brain and exerts its affects since angiotensin does not cross the blood brain barrier. Figure 8 depicts the 2 major

Fig. 8, Ref #8.



neuronal pathways for thirst, one operating via stimulation of osmoreceptors, the other via central angiotensin II receptors (8). Electrophysiologic studies have shown that in the brain there are neurons that respond to angiotensin alone and others that respond to acetylcholine alone (7). In certain areas there are neurons that respond to both acetylcholine and angiotensin. Carbachol, a cholinergic agonist evokes thirst when injected into rat brains (9). The effects are strikingly similar to angiotensin in dose and time order and also in producing a pressor response. The difference between stimuli is seen in sodium appetite. Angiotensin II given into the brain ventricle elicits a preference for hypertonic saline solution, but carbachol does not (10). Phillips et al (7) have postualted that there must exist parallel circuits for thirst involving angiotensin on the one hand and acetylcholine on the other. Thus cholinergic stimuli appear to mediate osmotic dehydration which does not require sodium intake, while angiotensin mediates hypovolemic dehydration which does. They demonstrated that neither a cholinergic nor an angiotensin antagonist alone could diminish drinking in rats deprived of water for 48 hours (Figure 9). However, the combination of antagonists to both

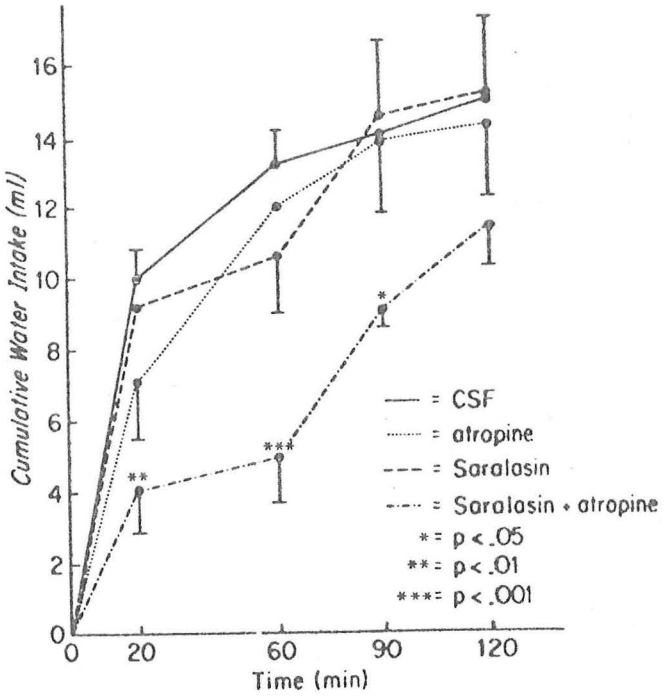


Fig. 9 Effect of cholinergic and angiotensin antagonists alone and in combination on drinking of rats deprived of water for 48 hours (11).

acetylcholine and angiotensin II (i.e. saralasin and atropine) diminished the drinking response (11).

CLINICAL DISORDERS OF THIRST

Types of thirst. Disturbances in thirst may be classified as either symptomatic or pathologic. Symptomatic thirst includes those cases in which thirst results from the loss of body water or electrolytes (Table 1).

Table 1

SYMPTOMATIC THIRST

Severe vomiting

Severe diarrhea

Central diabetes insipidus

Nephrogenic diabetes insipidus

Diabetes mellitus

Chronic renal failure

Sodium depletion

Potassium depletion

Hypercalcemia

Examples of this type of thirst include severe vomiting, severe diarrhea, true diabetes insipidus (a failure to release

antidiuretic hormone), nephrogenic diabetes insipidus, diabetes mellitus, certain forms of chronic renal failure, sodium depletion, potassium depletion, and hypercalcemia. In these situations thirst represents a normal physiologic reponse to a true water deficit. In the case of pathological thirst, a patient is thirsty despite the fact that the body is well hydrated or even over-hydrated (Table 2). Thus, pathological thirst represent an inappropriate activation of drinking.

Table 2

PATHOLOGICAL THIRST

Hypothalamic tumors, trauma, inflammation

Compulsive water drinking

High plasma renin concentrations

Hypokalemia

Hypercalcemia

Examples of pathological thirst include primary polydipsia caused by continued irritation of thirst neurons (e.g. tumor, trauma, inflammation), compulsive water drinking, high plasma renin levels, and direct stimulation of the thirst centers by hypokalemia or hypercalcemia. A defect in the intake limb of water balance, i.e. excessive or pathological thirst, will rarely if ever lead to an abnormality in body fluid tonicity (i.e. hyponatremia) providing that renal function and the mechanisms that regulate ADH secretion are intact. A patient with pure psychogenic polydipsia, normal kidneys, and no disorder of ADH secretion would be expected to have a normal serum sodium. It is estimated that the normal kidney has a capacity for free water excretion of between 600 and 1200 ml per hour. It is this tremendous capacity to excrete water that often makes it difficult to differentiate patients with compulsive water drinking from those with diabetes insipidus (12). Each group is characterized by polyuria, polydipsia, hypotonic urine, and reduced circulating levels of ADH. In evaluating a hyponatremic patient with psychogenic polydipsia it is important to evaluate also ADH-dependent causes of impaired water excretion.

Psychogenic polydipsia. Psychogenic polydipsia, also known as compulsive water drinking, potomania, and diposomania, is probably best described in the classic paper by Barlow and deWardener (12). They reported psychological disturbance in 8 of their 9 patients including hysteria, delusional hypochondriasis, and depression. The presenting complaint in most patients was increased thirst and polyuria. The

consumption of water fluctuated irregularly from hour to hour or from day to day and some patients had remissions that lasted several months or longer. This was an important differential point in distinguishing these patients from patients with diabetes insipidus in whom polydipsia and polyuria did not fluctuate over time. Another important distinguishing characteristic of the patients with compulsive water drinking was their lower plasma osmolality when compared to normals (Figure 10).

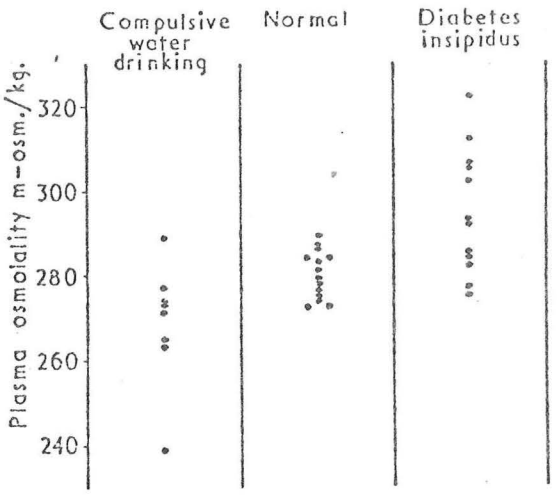


Fig. 10 Plasma osmolality in compulsive water drinking, in normal subjects, and in diabetes insipidus (12).

In contrast, 12 patients with diabetes insipidus had a significantly higher plasma osmolality than normal. In most patients with psycogenic polydipsia it is impossible to determine the cause of their abnormal drinking. Bizarre reasons are offered for such behavior including an attempt to flush out worms, poisons, or cancer. Other patients claim they are cleansing themselves of sin or are claming their nerves. Water intakes of as much as 43 liters per day have been recorded (13).

Many patients with compulsive water drinking have been schizophrenic and antipsychotic medications have been implicated in the pathogenesis of the abnormal drinking as well as stimulation of ADH release (14). Since many of the antipsychotic drugs are anticholinergic, a dry mouth has been suggested as a factor that would stimulate thirst. A number of the psychotropic drugs including thioridazine, fluphenazine, chlorpramazine, and haloperidol, have been linked to water intoxication in psychiatric patients, but a clear cause and effect relationship is lacking (14). Moreover, control of the acute psychosis with the use of psychotropic medications has been associated with resolution of the abnormal drinking behavior (13,15). Also, compulsive water drinking clearly

occurs in schizophrenic patients who are not being treated with antipsychotic medications (14).

All but one of the patients described by Barlow and deWardener (12) had a serum osmolality of greater than 260 mOsm/kg water. However, there are numerous reports of acute psychosis, polydipsia, and severe hypotonicity (hyponatremia) (13,14,16-21). The mechanism of hyponatremia in such patients is not always clear. Many of these patients have been described as having "pure water intoxication" or "SIADH". Before deciding whether these are apt descriptions of this disorder, it is worth examining how the normal osmoregulatory system deals with a water load. It is estimated that a normal individual can drink and excrete 20 to 24 liters of water a day and suffer no more than a 2 to 3 mOsm/kg depression in plasma osmolality. To accomplish this feat several requirements must be met (Table 3)

Table 3

Requirements for Maximal Water Excretion

1. Normal glomerular filtration rate
2. Adequate delivery of sodium to the diluting segment of the nephron
3. Absence of drugs that impair free water formation
4. Maximal suppression of antidiuretic hormone

The individuals must have: 1) normal glomerular infiltration rate, 2) adequate delivery of sodium to the diluting segment of a nephron (i.e. absence of conditions promoting increase proximal tubular sodium reabsorption, e.g. volume depletion, cirrhosis, congestive heart failure), 3) an absence of drugs that would impair the ability of the thick ascending limb to make free water (e.g. loop diuretics, thiazide diuretics) and 4) maximal suppression of antidiuretic hormone. Thus, in order to make a diagnosis of "pure water intoxication" a patient would have to satisfy the above criteria. The typical patient described as having pure water intoxication has had that diagnosis based on the findings of a low serum sodium at a time when the urine osmolality was appropriately depressed. A diagnosis of psychogenic polydipsia and SIADH is usually applied when hyponatremia occurs in the presence of a urine osmolality that is greater than plasma osmolality. Hariprasad et al (13) have offered an alternative to these two diagnostic possibilities. They studied 20 psychotic patients with psychogenic polydipsia and hyponatremia (serum sodium 94-124 mEq/L). These patients had a water intake of between 7 and 43 liters per day. Most of these patients had appropriately dilute urines (37-95 mOsm/kg) and positive free water clearances as a

result of their polydipsia. When water was withheld urine osmolality rose to greater than plasma osmolality and free water clearance became negative. The interesting finding of this study was that urine osmolality in 6 patients exceeded plasma osmolality (the point at which free water excretion stops) at a plasma osmolality that was clearly abnormally low, 240-272 mOsm/kg water (Figure 11).

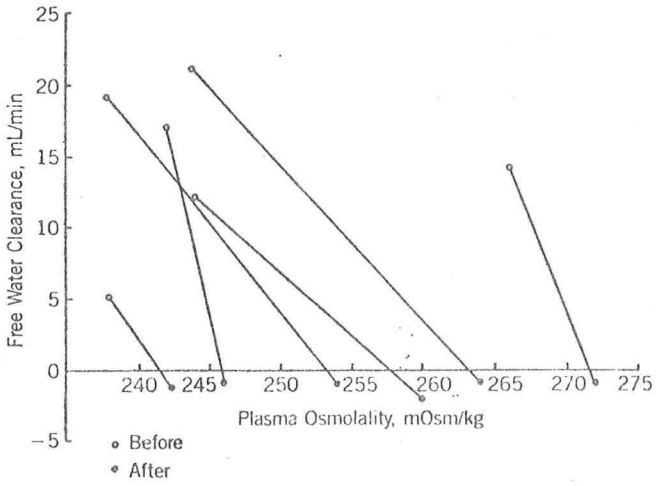


Fig. 11 Free water clearance and plasma osmolality before and after water deprivation in 6 patients with psychogenic polydipsia (13).

These findings were interpreted as consistent with a downward resetting of the osmostat. None of their 20 patients described excessive thirst. Seventeen of 20 patients were receiving antipsychotic medications. In 4 patients, increasing the doses of these drugs led to a resolution of the psychosis and the abnormal drinking behavior. A reset osmostat has been described in a number of chronic diseases including pulmonary tuberculosis (22), hypothyroidism (23), and cirrhosis of the liver (24). In these conditions patients are able to excrete a water load normally but plasma osmolality appears to have been reset at a lower level. It is probable that a "reset osmostat" represents a variant of SIADH (25). In such patients, plasma ADH is responsive to osmotic influences, but the set point of the system appears to be depressed. In some cases the entire osmoregulatory system including thirst appears to be reset.

Fig. 12 Reset osmostat in patient with oat cell lung cancer (2).

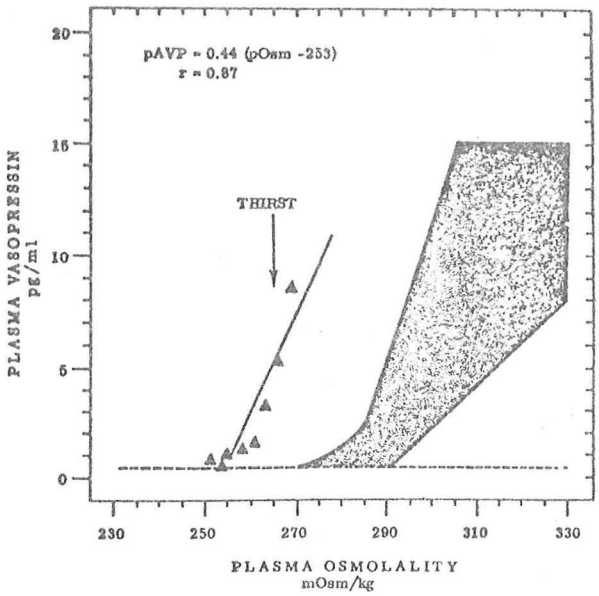
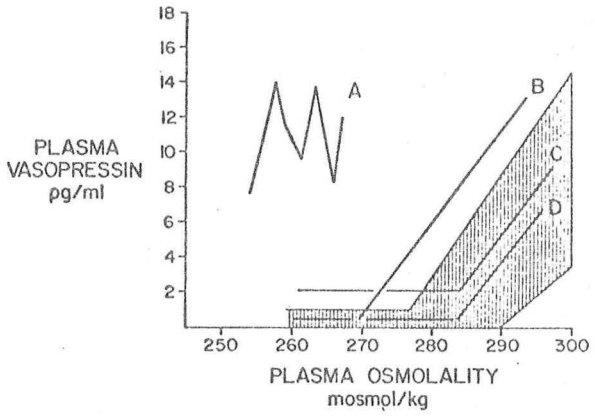


Figure 12 describes the relationship of thirst and plasma AVP to plasma osmolality in a patient with oat cell lung cancer and resetting of the osmostat. Figure 13 schematically depicts four types of osmoregulatory dysfunctions observed in the syndrome of SIADH (2). Type A represents the apparently random pattern of ADH secretion that occurs commonly in neoplastic disorders, but may also occur in non-neoplastic conditions. Type B represents "resetting of the osmostat". In such patients plasma ADH is responsive to osmotic influences, but the set point of the system is lowered. This type of patient would excrete a water

Fig. 13 Four types of osmoregulatory dysfunction (2).
See text for explanation.



load normally, but Type A would not. Type C patients have inappropriately high ADH levels under hypotonic conditions, but raise their ADH levels when plasma osmolality rises.

The clinical features of hyponatremia induced by psychogenic polydipsia include lethargy, disorientation, confusion, semi-coma or coma, and grand mal seizures. Laboratory data reveals a reduced serum sodium in the presence of either a low or inappropriately elevated urine osmolality. BUN is almost always low unless there is associated volume depletion. Raskin (17) described a fatal case of psychogenic polydipsia in which a 56 year old women with psychotic depression drank copious amounts of water and in a 24 hour period her serum sodium fell from 140 to 111 mEq/L. She developed breathing difficulty, bilateral decrebrate posturing, and suffered a respiratory arrest. Post-mortem examination revealed transtentorial herniation with generalized cerebral edema. The development of cerebral edema with rapidly developing hyponatremia is consistent with animal studies showing that brain water increases far more rapidly with an acute reduction in serum sodium than with a more slowly developing chronic reduction of serum sodium, Figure 14, (26).

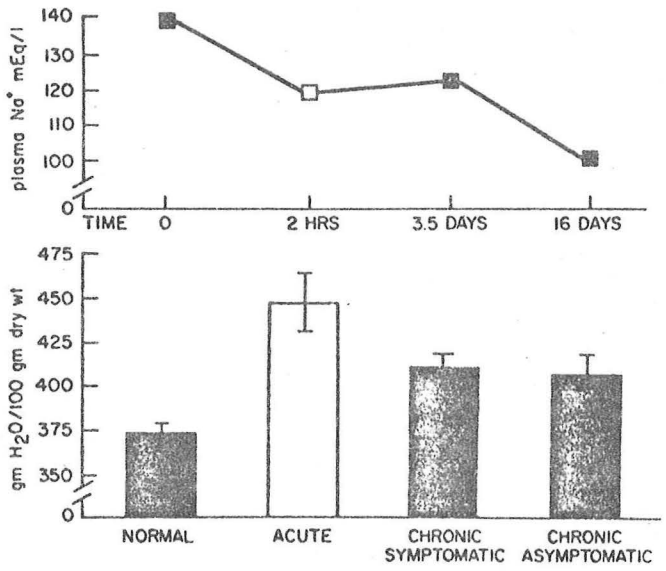


Fig. 14 Brain water in normal and 3 groups of hyponatremic rabbits (26).

Lastly, it is important to point out that a number of case reports have documented the danger in giving a thiazide diuretic to patients with polydipsia (13,14,16,17,20,21). Thiazide diuretics would be expected to impair water excretion in two ways: 1) induction of mild volume depletion which would stimulate release of antidiuretic hormone, and 2) impaired formation of free water in the distal nephron.

Psychogenic polydipsia at the DVAMC. Between 1977 and 1983 the Renal Consultation Service at the DVAMC evaluated 11 patients with symptomatic hyponatremia and a prominent disorder of thirst. The patients were variously described as having psychogenic polydipsia, water intoxication, and compulsive water drinking, or psychogenic polydipsia and SIADH. In this group of patients there were a total of 70 hospitalizations for this problem with the range being 24 hospitalizations in 1 patient and single hospitalizations in 3 patients. At the time of admission none of the patients was confined to a long term psychiatric facility. Ten patients were male, 1 was female. The ages ranged from 42 to 67 with a mean age of 56.8 years (Table 4). Six of the male patients were black, 4 were white, and the female patient was white. The duration of compulsive water drinking in the 11 patients range from 1 week to 43 years.

Table 4

Hyponatremic Psychogenic Polydipsia: DVAMC

Patient	Sex	Race	Age	#Hospitalizations	Duration of polydipsia
1	M	B	60	24	11 y
2	M	B	67	10	4 y
3	M	B	56	15	7 y
4	M	B	66	1	1 m
5	M	W	62	5	?
6	M	W	59	3	43 y
7	M	B	42	1	12 y
8	M	B	54	3	3 y
9	M	W	50	2	1 y
10	F	W	48	1	1 w
11	M	W	61	5	10 y

Weakness, lethargy, nausea, vomiting, and hiccups were common complaints (Table 5). The past history of the patients showed many

Table 5

Hyponatremic Psychogenic Polydipsia: DVAMC

Chief Complaint	lethargy	(6)
	nausea	(3)
	vomiting	(6)
	hiccups	(5)
Related Disorders	Chronic alcoholism	(10)
	Intractable hiccups	(7)
	Self-induced vomiting	(6)
	Thiazide diuretics	(3)
	Schizophrenia	(3)
	Organic brain syndrome	(3)
	Hypertension	(5)
	Peptic ulcer disease	(5)
	Sliding hiatal hernia	(2)
	SIADH 2^{o} pulmonary TB	(1)
Complications	Grand mal seizures	(8)
	Volume depletion	(3)
	Metabolic alkalosis	(3)
	Rhabdomyolysis	(5)
	Adynamic ileus	(1)

features in common. Ten of 11 patients had a history of alcoholism, although it was only a prominent feature at the time of hospital admission in 3. None of the patients complained of thirst. Seven patients complained of intractable hiccups. For these 7 patients, hiccups were the primary reason they drank excessive quantities of water. In 2 of the patients, a family member (the father in one case, a brother in another) also suffered from intractable hiccups. The duration of hiccups ranged from 2 to 37 years. In 10 patients, 7 with chronic hiccups and 3 without

hiccups, vomiting frequently was a factor involved in the excessive water intake. Six patients induced vomiting concurrently with increased water intake. In 5 patients with chronic hiccups, self-induced vomiting was a measure used to stop the hiccups. Three patients were receiving a thiazide diuretic at the time of admission for hyponatremia, and in one of these patients the development of hyponatremia coincided with starting the diuretic. Three patients were diagnosed as schizophrenic and 3 patients were diagnosed as chronic alcoholics with resulting mild to moderate organic brain syndrome. Other disorders that occurred commonly in these patients were hypertension (5), peptic ulcer disease (5) and sliding hiatal hernia (2).

A variety of complications resulted because of this disordered drinking behavior. Eight patients had grand mal seizures prior to admission or shortly after admission on 1 or more occasions. In 5 of the patients with seizures, factors in addition to severe hyponatremia could be implicated in the genesis of the seizures; 4 patients had had documented alcoholic withdrawal seizures, and 1 patient had had seizures following head trauma. Clinically apparent volume depletion, often with metabolic alkalosis, was a common feature in the admissions of 3 patients, but was not consistently found in any of the other 8 patients. Five of 11 patients had a total of 19 episodes of rhabdomyolysis based on an elevation of the serum creatine phosphokinase. In only 6 of these 19 episodes was a grand mal seizure documented. Adynamic ileus was present at the time of admission twice in the same patient. In each case, the ileus resolved when the serum sodium returned to normal. A composite of the laboratory data for these patients is shown on Table 6. Based on the lowest value recorded for specific gravity or urinary osmolality, 8 of 11 patients were clearly capable of excreting a dilute urine, Table 7.

Table 6

Serum Electrolytes, Creatinine, BUN

Patient	n	ADMISSION						RECOVERY					
		Na	K	Cl	CO_2	BUN	Cr	Na	K	Cl	CO_2	BUN	Cr
		mEq/L				mg/dl		mEq/L				mg/dl	
1	24	114 ±4	2.8 ±1.0	64 ±10	34 ±7	31 ±13	2.1 ± 1.5	138 ±4	4.5 ±1.0	99 ±7	28 ±4	21 ±11	1.6 ± 0.3
2	10	107 ±6	3.7 ±0.5	70 ±11	21 ±4	13 ± 7	1.1 ± 0.2	137 ±2	4.4 ±0.7	98 ±3	25 ±3	13 ± 8	1.3 ± 0.1
3	15	112 ±7	4.1 ±0.6	74 ±8	23 ±5	5 ± 4	1.0 ± 0.2	135 ±6	4.4 ±0.6	98 ±5	26 ±3	7 ± 4	1.1 ± 0.2
4	1	117	3.4	81	24	17	1.6	136	5.2	101	27	22	1.4
5	5	123 ±7	2.5 ± 0.6	71 ±12	38 ±3	10 ± 6	1.2 ± 0.2	140 ±5	4.5 ±0.4	102 ±3	28 ±3	12 ± 1	1.3 ± 0.1
6	3	117 ±3	3.6 ± 0.5	80 ±6	25 ±1	42 --	3.0 ± 1.4	128 ±3	4.0 ±0.3	95 ±2	23 ±2	28 ± 9	2.5 ± 0.6
7	1	120	2.6	87	28	4	0.5	132	4.4	97	28	3	0.9
8	3	119 ±7	3.2 ± 0.7	73 ±3	31 ±6	35 ±15	1.9 ± 1.1	131 ± 1.5	4.4 ±0.9	95 ±1	24 ±3	10 ± 1	0.8 ± 0.1
9	2	115	3.8	81	21	3	0.9	137	3.8	101	26	5	1.0
10	1	115	3.6	81	13	5	0.7	140	4	115	22	3	0.6
11	5	112 ±7	3.9 ± 1.3	70 ±16	27 ±5	11 ± 5	0.8 ± 0.2	137 ±4	4.4 ± 0.1	98 ±4	27 ±3	-- --	0.9 ± 0.3

$\bar{x}$ ± S.D.

Table 7

Urinary Concentration

Patient	High Specific Gravity	Uosm	Low Specific Gravity	Uosm
1	1.010	530	1.003	90
2	1.012	343	1.003	50
3	1.011	423	1.002	122
4	1.007	---	1.003	165
5	1.021	276	1.006	---
6	1.010	---	1.004	102
7	-----	421	1.002	117
8	1.024	---	1.008	---
9	-----	---	1.002	54
10	-----	---	1.002	45
11	1.026	---	1.008	238

One feature that distiniguishes this group of psychogenic polydipsic patients from previous reports is the high prevalence of hiccups and self-induced vomiting. For most of these individuals, self-induced vomiting and excessive water drinking represented an attempt to alleviate hiccups. These are features that previously have not been described in psychogenic polydipsia. The reason for this difference is not readily apparent, but several differences in the study population may be important. Most previous reports of compulsive water drinking have dealt with institutionalized psychiatric patients, whereas the patients described here were not. These patients had a strong history of alcohol abuse and often had evidence suggesting and supporting the presence of organic brain disease. Only one of the patients typlified the schizophrenic compulsive water drinker (Patient 9). Thiazide diurectics were being taken by three of the patients (#2,4,8) at the time of admission. The importance of this agent as a complicating factor in patients with compulsive water drinking was mentioned earlier.

Intractable hiccups is an uncommon disorder which has been attributed to various etiologies. It has a strong male predominance (27). Hiccups represent intermittent reflex clonic spasms of one or both hemidaphragms associated with glottic closure (28,29). The list of etiologic factors thought to be important in intractable hiccups is long and diverse and says more about our lack of understanding of this condition then it does about hiccups themselves (Table 8). Attempts to treat this

Table 8

Causes of Hiccups

Intraabdominal

a. Gastric dilatation

b. Intraabdominal inflammation, hemorrhage, surgery

c. Subdiaphragmatic abscess

Neck-Thorax

a. Compression of phrenic nerve

b. Pneumonia

c. Diaphragm tumor

d. Myocardial infarction

e. Esophageal disease

f. Tumor

Central Nervous System

a. Trauma

b. Infection

c. Vascular insufficiency

d. Cerebrovascular accident

e. Tumor

f. Uremia

Ref #29

disorder have generally been disappointing. A number of centrally and peripherally acting drugs have been tried with little success (30). Non-drug treatment modalities have also been used (Table 9). Lastly, a number of folk remedies have

Table 9

Non-Drug Treatments of Intractable Hiccups

1. Granulated sugar
2. Stimulation of oropharynx
3. Phrenic nerve stimulation, injection, or crushing
4. Hypnosis
5. Acupuncture

Ref #30

been suggested (Table 10). Since these patients often hiccup 20 to 30 times per minute for months or years, it is easy to

Table 10

Folk Remedies for Intractable Hiccups

1. Sneezing induced with pepper or snuff
2. Honey and vinegar
3. Breath holding
4. Rebreathing into a paper bag.
5. Drinking water while covering the ears tightly
6. Drinking from the "wrong side" of a cup
7. Sudden fright
8. Traction on the tongue

Ref #30

understand how such remedies might be tried by a patient desperate for relief. In our patients, oropharyngeal stimulation with a finger or in one case a spoon to induce vomiting was used repeatedly to stop hiccups. A promising new drug therapy has been reported recently by Jacobson et al (31).

Since hiccups have been considered a form of myoclonus and valproic acid is effective in treating several forms of myoclonus, they used it to treat five patients with intractable, incapacitating hiccups. Symptoms were eliminated in four and markedly improved in the fifth.

The mechanism of development of hyponatremia in these patients was not investigated in a prospective manner. However, several observations can be made about the pathogenesis of the hypoosmolality. As discussed earlier, "pure water intoxication" is an unlikely explanation for the hypoosmolality. It is probable that in all of the patients presented here, antidiuretic hormone was involved in generating the hyponatremia. Four patients were clearly volume depleted as a result of self-induced vomiting and through this mechanism presumably stimulated ADH. An important role for vomiting in the pathogenesis of hyponatremia was confirmed in several patients by the demonstration of a high plasma bicarbonate, a low urinary chloride, and a high BUN that fell with treatment. One patient (#11) carried the diagnosis of chronic SIADH for 9 years. This diagnosis was supported by the patient's euvolemic status, hyponatremia, hypouricemia, and urine osmolality that was consistently greater than plasma osmolality. While all but one of the remaining patients demonstrated a capacity to excrete a dilute urine at sometime in their course thus demonstrating an ability to suppress ADH release, it is nevertheless likely that these patients had a form of SIADH. Two potential mechanisms, singly or in combination, could have been operative: 1) resetting of the osmostat and/or 2) non-osmotic stimulation of ADH. The possibility of a reset osmostat, discussed earlier, certainly exist in the patients presented here, but a role for non-osmotic stimulation of ADH cannot be excluded. In particular, two non-osmotic factors may have been involved. Rowe et al (32) demonstrated the frequent association of nausea and vomiting with striking elevations of plasma vasopressin. Using pharmacologic probes, they concluded that nausea was the primary factor mediating the rise in vasopressin. Figure 15 demonstrates the effect of apomorphine-induced nausea in a patient undergoing volume expansion and a water diuresis. Recall from Figure 3 that plasma AVP levels of 5 pg/ml are sufficient to produce maximally concentrated urine. Nausea was a common complaint in the patients described here. It is interesting to speculate that chronic intractable hiccups might also be a non-osmotic stimulus to ADH release. There is at the present time data to support to refute this hypothesis.

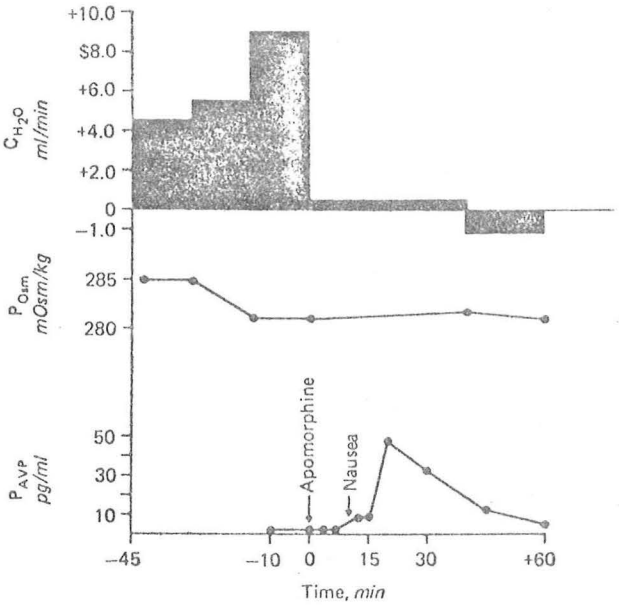


Fig. 15 Relation of apomorphine-induced nausea and AVP release to free water clearance in human subjects undergoing water diuresis (32).

Symptoms and signs of skeletal muscle dysfunction were common in these 11 patients. Lethargy and weakness were frequent complaints and serum creatine phosphokinase (CPK) was elevated on 19 of the 70 episodes (27%). Since CPK was not routinely ordered in these patients, this figure is probably an underestimation of the incidence of rhabdomyolsis. The mechanism responsible for rhabdomyolysis in these patients was probably multifactorial. Many of the patients had grand mal seizures as a result of their hyponatremic state, but this was documented in only 6 of 19 of the episodes. Muscle cells swell during hyponatremic states (26) and like brain, lose sodium and potassium to the extracellular compartment. While electrolyte losses may reduce cell swelling, the lowered cell electrolyte content may impair cell metabolism and membrane transport functions to such a degree that cell injury and necrosis occur.

Case Report

Patient #1. A 60 year old black male, retired mechanic, had a history of symptomatic hyponatremia dating to 1968. At about that time he developed intractable hiccups. During the period from 1973 to 1981 he had 24 admissions to the Dallas VAMC and multiple additional admissions to other VAMC's in the state of Texas for volume depletion, severe hyponatremia, and metabolic alkalosis. The interval between admissions was often as short as 3 to 5 days. His chief complaint in the early years was "hiccups, weakness, nausea, and vomiting", but after having established an almost monthly pattern of admissions for these same symptoms his chief complaint became simply "I think my sodium is low". The patient reportedly drank up to 10 to 12 gallons of water per day to relieve his hiccups. While he insisted that hiccups initiated the water drinking, his wife related that the process began as self-induced vomiting, often with a spoon, followed by excessive water drinking, followed by hiccups. Past medical history included the following diagnoses: essential hypertension, glaucoma, latent lues, upper gastrointestinal bleeding, colonic diverticuli, and alcohol abuse. At the time of admission, he typically had a flat affect and was occasionally confused, but usually was oriented to person, place, and time. Blood pressure was always low and volume depletion was invariable present. Despite the marked hyponatremia no seizures were ever reported. Laboratory data on a typical admission (4-6-79) showed a serum sodium of 113 mEq/L, potassium 2.5 mEq/L, chloride 66 mEq/L, bicarbonate 42 mEq/L, BUN 43 mg per deciliter, serum creatinine 2.2 mg per deciliter, urinary sodium 18 mEq/L, urinary chloride 0 mEq/L, urinary potassium 28 mEq/L. Since the patient rarely exhibited serious neurological deficits at the time of admission, the standard treatment became water restriction and IV saline administration. With this treatment, serum electrolytes normalized within a few days. With elevation of the serum sodium to the normal range, hiccups usually abated. On several occasions when this treatment plan failed to completely normalize his serum sodium, the patient was discovered inducing vomiting and drinking large quantities of water. Attempts to restrict the patient's access to water by turning off the sink faucets in his room were usually ineffective measures, since the patient was found drinking water from sinks in the rooms of other patients or the commode. Repeated psychiatric consultations, hypnosis, and psychoactive drugs including thorazine and valium failed to change the patient's drinking behavior. The patient refused to cooperate with any long term psychiatric treatment program. Since 1972 the patient has received Social Security Disability payments for hiccups.

Patient #2. A 66 year old black male was admitted to the VAMC Dallas on 7-20-81 with a history of intractable hiccups. He had had 7 previous admissions for a similar complaint, often

associated with nausea and vomiting, and on one occasion a probable seizure. His stated reason for drinking as much as 2 to 3 gallons of water per day was to cure his hiccups. Other medical problems included essential hypertension and hypertensive cardiovascular disease. On two of these admissions he developed adynamic ileus that resolved with correction of the hyponatremia. On physical examination, he was usually alert but disoriented and exhibited constant "hiccupping, growling, grunting, and spitting". Laboratory data revealed profound hyponatremia. On 7 of 8 admissions he was noted to have an elevated CPK, but on only one of these occasions did the patient have what might have been a seizure. Treatment of the hyponatremia consisted of water restriction and either isotonic or hypertonic saline. In May of 1980 the patient had a normal water loading test. Although he was treated with thorazine, it had little effect on the frequency of his hiccups. He expired on January 9, 1982 of unknown causes.

Patient #3. A 56 year old black male former construction worker gave a 30 year history of chronic hiccups which he treated by inducing vomiting and drinking large quantities of water. In addition, the patient's past medical history included a long history of heavy alcohol abuse, probable alcoholic cerebellar degeneration, a partial gastrectomy for peptic ulcer disease, lumbar disc surgery, and a right cerebrovascular accident with mild residual left hemiparesis. Between 1976 and 1983 he had 16 admissions that were precipitated by a complaint of hiccups and symptomatic hyponatremia and often accompanied by grand mal seizures. At the time of admission, the patient's serum sodium was as low as 103 mEq per liter. Chronic thorazine therapy for hiccups gave the patient little relief. He admitted to heavy and regular alcohol abuse averaging 1 pint of gin per day for 15 years. Physical examination on a typical admission revealed a muscular black male who was usually intoxicated, agitated and uncooperative. Occasionally he presented in semicoma or was postictal. The remainder of the physical examination was generally unremarkable. Repeated evaluations of the patient's seizure disorder were negative including the following studies: skull films, lumbar puncture, electroencephalogram, brain scan, and computerized axial tomography of the head. The presumed etiology of the seizures was severe hyponatremia, but a contribution from alcohol withdrawal could not always be excluded. Treatment of the hyponatremia usually consisted of water restriction and isotonic saline infusion, but a few episodes were treated with hypertonic saline and furosemide diuresis. In addition, at various times during this period he was noted to have a normal water load test, a normal serum cortisol, normal growth hormone and prolactin levels, normal thyroid function tests, and a normal sphenoidal electroencephalogram with sleep studies. The patient had no insight into his disease and frequently complained to

nurses and physicians that he needed more water. Restricting the patient's water was difficult. Locking the bathroom door in the patient's hospital room resulted in a scorched wall following an attempt by the patient to burn the door open. Although water restriction in the hospital was successful in restoring serum sodium to the normal range, chronic hiccups continued to be a problem.

Treatment of psychogenic polydipsia. In patients with psychogenic polydipsia and severe psychiatric disturbances, it is virtually impossible to influence the intake of water without treating the underlying psychiatric disease. In most reports, the treatment of the underlying psychosis with antipsychotic drugs led to a lessening of the polydipsia (13). If medications fail to control the psychosis, attempts to restrict access to water without the patient's cooperation are usually unsuccessful. Such patients will go to any extreme to obtain water. In practical terms, a serum sodium that remains in the range of 122-126 mEq/L on a chronic basis probably need not be treated provided the patient is asymptomatic. Since it is likely that inappropriate secretion of antidiuretic hormone participates in most if not all cases of hyponatremic psychogenic polydipsia, therapies that stimulate further the secretion of antidiuretic hormone should be avoided. In particular, thiazide diuretics should be avoided because of their prolonged action and their known effect to impair the formation of free water. If a diuretic agent is necessary, a trial with a shorter acting loop diuretic such as furosemide may be successful. Although furosemide also impairs the formation of free water, its shorter duration of action makes it theoretically less likely to produce hyponatremia.

Acute treatment of hyponatremia in psychogenic polydipsia. The therapy of hyponatremic psychogenic polydipsia must be dictated by the clinical state of the patient as well as by the etiology of the disorder. The signs and symptoms of symptomatic hyponatremia are listed on Table 11. The aggressiveness of

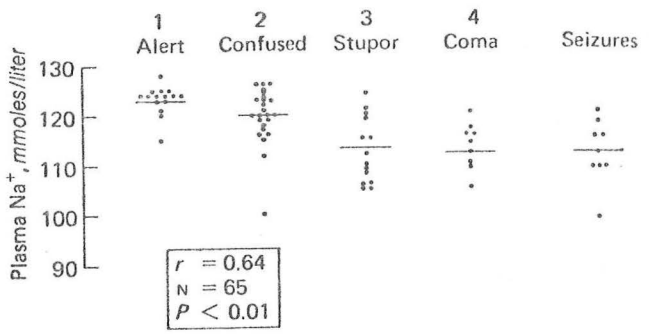
Table 11

Hyponatremia

Symptoms	Signs
Lethargy	Abnormal sensorium
Apathy	Depressed reflexes
Disorientation	Cheyne-Stokes respirations
Muscle cramps	Hypothermia
Anorexia	Pathological reflexes
Nausea	Pseudobulbar palsy
Agitation	Seizures

therapy should be matched to the severity of the signs and symptoms. A patient complaining of lethargy, disorientation, and nausea with a serum sodium of 115 mEq per liter and a dilute urine might be expected to correct rapidly with water restriction and saline expansion alone. In contrast a patient with pathological reflexes and seizures, a serum sodium of 103 mEq/L, and a concentrated urine will need more aggressive therapy such as hypertonic saline and possibly a loop diuretic to stimulate the removal of free water (33). Restoration of serum sodium to levels above 125-130 mEq per liter is usually sufficient to correct the acute symptoms and signs of hyponatremia. Figure 16 demonstrates the relationship between

Fig. 16 Relationship between plasma sodium and depression of sensorium (34).



plasma sodium concentration and depression of sensorium in 65 patients with plasma sodium of 128 mEq/L or less (34). In patients who had seizures, the mean plasma sodium was 112±2 mEq/L, while in those patients who did not have seizures, plasma sodium was 119±1 mEq/L. The necessity for rapid correction of symptomatic hyponatremia has recently been questioned because of reports that central pontine myelinolysis may be precipitated by this approach.

Central pontine myelinolysis. Central pontine myelinolysis is a frequently fatal disorder often associated with hyponatremia. Some authors have suggested that vigorous correction of hyponatremia may be more damaging than the hyponatremia itself (35-37). Wright et al (38) noted that vigorous corrective efforts for severe hyponatremia had been documented in many of the cases with extrapontine myelinolysis. Burcar et al (39) drew attention to the possible role of hyponatremia in the pathogenesis of central pontine myelinolysis when they reported that hyponatremia (less than 130 mEq per liter) was present in all 15 patients in their series and in 12 of 30 reported cases in which serum sodium values had been recorded. However, hyponatremia is not a universal finding in central pontine myelinolysis. In fact, some cases are characterized by hypernatremia rather than hyponatremia (38,40). Laureno (41) studied the problem of pontine and extrapontine myelinolysis experimentally in dogs by rapidly correcting severe, sustained, vasopressin-induced hyponatremia. Correction of hyponatremia with water restriction alone was not associated with myelinolysis in 5 of 6 animals. In the one affected dog, the lesion was mild. However, in 5 of 10 animals in which hyponatremia was rapidly corrected by the infusion of hypertonic (3%) saline, autopsy demonstrated pontine and extrapontine myelinolysis. The 5 other dogs had normal brains at autopsy. The investigator concluded that the rate of correction of hyponatremia appeared to be the critical variable determining whether myelinolysis would occur. Thus, central pontine myelinolysis may be an iatrogenetic disease. One report suggested that this was a new disease resulting from some change in medical practice (42). Factors implicated in the manifestation of this presumably new disease entity included the introduction of thiazide diuretics, the ability to measure serum sodium as a routine clinical test, and therapeutic efforts to correct sodium derangements.

In summary, symptomatic hyponatremia with stupor or seizures is a medical emergency requiring immediate treatment. Robertson (43) recently reported good success in treating such patients with hypertonic saline (5% Na Cl at a rate of 0.05 ml/kg/min) until serum sodium has risen approximately 7 mEq/L. No adverse neurologic effects have resulted from this approach. While the issue is far from settled, the development of central

pontine mylenolysis may depend both on the rate at which the serum sodium is raised and the absolute level achieved. Neural cells appear to be most vulnerable when water and electrolyte contents are changing rapidly (34). Acute water intoxication developing over a 24 hour period has a mortality rate of 50% (26). Thus, the rapid development of hyponatremia is more likely to lead to central nervous system symptoms and signs than the gradual development of hyponatremia. Conversely the rapid correction of a chronically low serum sodium is probably more likely to create neurological symptoms than a more gradual correction.

Hypodipsia. Patients who exhibit chronic hypernatremia invariably have a defect in thirst. In addition, these patients commonly have a defect in antidiuretic hormone secretion. Table 12 lists the factors that are known or suspected to cause hypodipsia (2). The disorder results most commonly, from

Table 12

Hypodipsia

Primary
- Osmoreceptor damage (adipsic hypernatremia)
  - complete
  - partial
- Osmoreceptor reset? (essential hypernatremia)

Secondary
- Hemodynamic (hypervolemia)
  - Primary hyperaldosteronism

osmoreceptor damage and is known as adipsic hypernatremia. The condition is due to a destruction of the osmoreceptor, since these patients do not experience thirst at any level of hyperosmolarity. Table 13 lists the specific causes of adipsic hypernatremia. Because the osmoreceptors for thirst and ADH

Table 13

Specific Causes of Adipsic Hypernatremia

- Vascular (15%)
  - Anterior communicating artery
    - Aneurysms
    - Ligation
  - Intrahypothalamic hemorrhage
  - Internal carotid ligation
- Neoplastic (50%)
  - Primary
    - Craniopharyngioma
    - Pinealoma
    - Meningioma
    - Chromophobe
  - Metastatic
    - Lung
    - Breast
- Granulomatous (20%)
  - Histiocytosis
  - Sarcoidosis
- Miscellaneous (15%)
  - Hydrocephalus
  - Ventricular cyst
  - Trauma
  - Idiopathic

Ref #2

are in such close proximity, adipsic hypernatremia is commonly associated with a defect in ADH secretion. Figure 17 describes

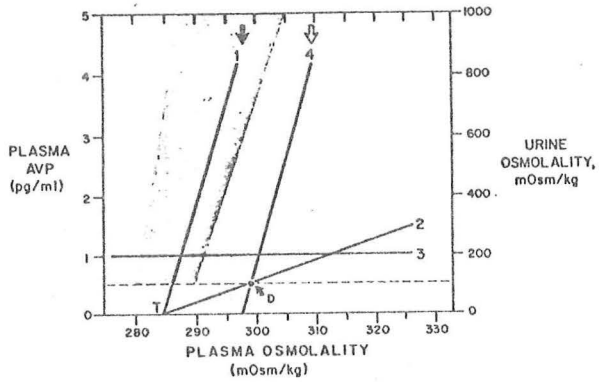


Fig. 17 Osmoregulatory abnormalities in patients with hyperosmolar syndrome (2).

the osmoregulatory abnormalities observed or postulated in patients with hyperosmolar syndromes. The numbered lines depict the relationship of plasma ADH to osmolarity. Line 1 represents healthy adults, line 2 represents patients with adipsia and partial destruction of the osmoreceptor. In this condition ADH secretion remains responsive to changes in osmolality, but the slope or gain of the system is markedly reduced. Because of this and the associated hypodipsia, the individual is unable to respond quickly or completely to changes in water balance and consequently experiences extreme degrees of body fluid hypertonicity. Line 3 represents patients with hypodipsia and complete destruction of the osmoreceptor. In these patients ADH is unresponsive to changes in body fluid osmolarity, but responds normally to hemodynamic and other non-osmotic stimuli to ADH release. Line 4 represents the hypothetical relationship between plasma ADH and plasma osmolality in patients with essential hypernatremia or what is sometimes called "resetting of the osmostat". These terms have been used to explain certain hypernatremic syndromes which lack physical signs of volume depletion and in which the patients may dilute the urine at abnormally high levels of plasma osmolality. Since careful measurements of ADH have not been made in this disorder it may be that most cases of essential hypernatremia in fact represent partial destruction of the osmoreceptor (line 2). However, a resetting upwards of the osmostat is know to occur in certain other conditions. For example, the osmotic threshold for thirst and ADH release are elevated in patients with primary hyperaldosteronism. The resetting appears to be a consequence of the marked hypervolemia induced by the excess of aldosterone.

Miller et al (44) reported that hypodipsia may occur in elderly patients without demonstrable hypothalamic or pituitary lesions. They described 6 elderly patients who had had cerebral vascular accidents and recurrent hospitalizations for dehydration and hypernatremia. Despite a normal mental status exam none of the patients was thirsty. The mean plasma osmolality for the group was 363 mOsm/kg water (Table 14). All

Table 14

Hypodipsia in Geriatric Patients

	S_{Na} (mEq/L)	P_{osm} (mOsm/L)		Weight (kg)		BUN (mg/dl)	
	pre	pre	post	pre	post	pre	post
1	158	347	285	58	62.5	65	26
2	165	368	282	47	52	88	28
3	172	383	280	51	57	78	21
4	161	353	276	49	54.5	64	17
5	152	361	285	61	66.5	95	24
6	166	368	284	70	73.5	84	14
$\bar{x}$	162	363	282	56	61	79	22

Ref #44

of these patients were volume depleted and thus had the two known stimuli for thirst (hyperosmolality, hypovolemia). The important therapeutic lesson to be taken from this report is that such patients cannot be managed simply by encouraging water intake, but rather must have water prescribed on a periodic basis.

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