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WATER HOMEOSTASIS

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INTRODUCTION

Stability of composition and volume of body fluids is of paramount importance for the survival and function of a living organism. This stability of the internal environment (known as homeostasis) is maintained through a series of feedback mechanisms that, in response to relatively small changes in physiologically important variables, set into motion events that will promptly restore the altered variable to the normal level. One of the best examples of a perfectly functioning homeostatic system is water balance, which is maintained despite the large variations in water intake and loss that occur under normal circumstances. The mechanisms involved in preserving the water balance and their most common derangements are the subjects of this review.

To understand water balance, it is important to know the basic quantitative aspects of water distribution among various tissues. Water is certainly the largest constituent of the human body, representing about 60% of body weight or about 42 liters in a 70-kg person (25, 36). Approximately 65% of total

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body water (or 27 liters in a 70-kg person) is intracellular. The remaining 15 liters represent extracellular water, which is further divided into a smaller intravascular (plasma) and a larger extravascular (interstitial) compartment. Since plasma is in a constant equilibrium with extracellular fluid, the composition of the two remains similar in practically all situations. Therefore, the concentrations of various substances measured in plasma may be considered to represent those of the extracellular fluid in general.

The solute compositions of intracellular and extracellular fluids are markedly different (36), primarily because most cell membranes possess transport systems that accumulate or expel specific solutes. However, because most cell membranes are freely permeable to water, the *total* solute concentration is very similar in the two compartments (18, 36). The total solute concentration is usually measured by determining the freezing point and is expressed as osmolality (solute concentration in a kilogram of water). Measured osmolality should, however, be differentiated from effective osmolality, i.e. the concentration of solutes that will create an osmotic force in vivo. The effective osmolality in a given compartment depends on the concentration of substances that are restricted to that compartment. Thus, sodium is the major determinant of the effective osmolality of plasma and other extracellular fluids because its concentration in that compartment is high, relative to other solutes, and because it is restricted from entering into cells (36, 58). In contrast, urea, which permeates the cells freely, will not exert an osmotic force if elevated in either compartment. The osmotic effectiveness of glucose vis-à-vis a certain tissue depends on whether glucose can enter that tissue under a given circumstance. Glucose enters some tissues by passive diffusion and others by an insulin-mediated transport system. If glucose concentration rises while insulin is deficient, a concentration gradient will develop across insulin-dependent cells such as those of skeletal muscle or fat but will not develop across brain or liver cells, which are freely permeable to glucose even in the absence of insulin. Thus, in the absence of insulin, an increase in extracellular fluid glucose causes an effective osmotic shift of water from insulin-dependent cells. This illustrates that the effective osmolality of plasma and other body fluids depends not only on the concentration of various solutes but also on the permeability of cell membranes to these solutes.

The extracellular fluid is in a state of constant exchange with the environment, as a result of which its content of water and solutes is subject to continuous change. However, because most cell membranes are freely permeable to water, altering the osmolality of the extracellular fluid changes the osmolality as well as the volume in the intracellular fluid. In other words, the cell volume, which is essential for its survival, is critically dependent on the osmolality of the extracellular fluid. Since most cells cannot tolerate

significant volume changes, it is clear that maintaining the osmolality of the extracellular fluid is of paramount importance for normal biological function. This is probably why an elaborate system has evolved to ensure near constancy of the extracellular fluid osmolality despite wide variations in the intake of solutes and water.

The extracellular fluid osmolality in man and other mammals is maintained through the precise regulation of thirst and secretion of the antidiuretic hormone arginine vasopressin (56, 58). Thus, an increase in extracellular osmolality stimulates thirst and vasopressin secretion, which leads to intake of water as well as a decrease in urinary water loss. The resulting increase in the water content of the extracellular fluid promply restores its osmolality to the previous level. Conversely, overhydration decreases plasma and extracellular fluid osmolality and suppresses vasopressin secretion. As a result, dilute urine is excreted, water surplus lost, and extracellular fluid osmolality returned to normal.

Another physiologically important consequence of effective osmoregulation is that the absolute amount of water in the extracellular fluid, and therefore its volume, is determined by its sodium content. Thus, if sodium is added to the extracellular fluid, the osmolality rises and results in water intake and a decrease in urinary water loss that returns the osmolality to the previous level but increases the extracellular fluid volume. Conversly, if sodium is lost in excess of water, the osmolality falls, which leads to excretion of solute-free water and restoration of osmolality. However, the total volume of plasma and extracellular fluid will decrease.

While keeping the extracellular fluid osmolality in a narrow range is essential for cell survival, maintaining plasma volume within a somewhat wider range is important for the normal function of the circulatory system, tissue perfusion, and delivery of nutrients and oxygen. Therefore, complicated integrative mechanisms, which include the volume and pressure receptors of the heart and blood vessels, the endocrine system and the kidney, have developed to regulate sodium balance and through that maintain normal circulating plasma volume (50).

NORMAL REGULATION OF WATER BALANCE

Antidiuretic Hormone

ANATOMY, BIOSYNTHESIS, AND SECRETION The antidiuretic hormone of humans and most other mammals is arginine vasopressin. It is produced by the neurohypophysis, an elongated extension of the ventral hypothalamus attached to the dorsal and caudal surface of the adenohypophysis. The upper hypothalamic part, referred to as the infundibulum or median eminence, is connected by a short stalk to the lower part, known as pars nervosa of the

pituitary gland. The secretory elements of the neurohypophysis are neurosecretory axons originating in magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus (70). While many axons project to the pars nervosa, some terminate in more proximal structures, including the infundibulum. This explains why even a complete section of the stalk frequently does not cause a complete deficiency of the antidiuretic hormone (56).

Vasopressin is synthesized in the form of propressophysin, with a molecular weight of approximately 20,000 (64, 82). The prohormone is synthesized in the cell bodies of the supraoptic and paraventricular nuclei, packaged in the granules, transported down the axons, and stored in the nerve terminals of pars nervosa. As the secretory granules move down the axons, the propressophysin is progressively cleaved to yield the active hormone vasopressin (~1100 daltons) and the inactive component neurophysin (61). Vasopressin and neurophysin are released by a calcium-dependent exocytotic process commonly seen in neurosecretory tissues.

REGULATION OF VASOPRESSIN SECRETION

Osmoregulation Under physiological conditions, vasopressin secretion is regulated primarily by plasma osmolality (58, 60). The functional properties of the osmoregulatory system can be understood from Figure 1*a*, which shows the relationship of plasma vasopressin to plasma osmolality in healthy adults

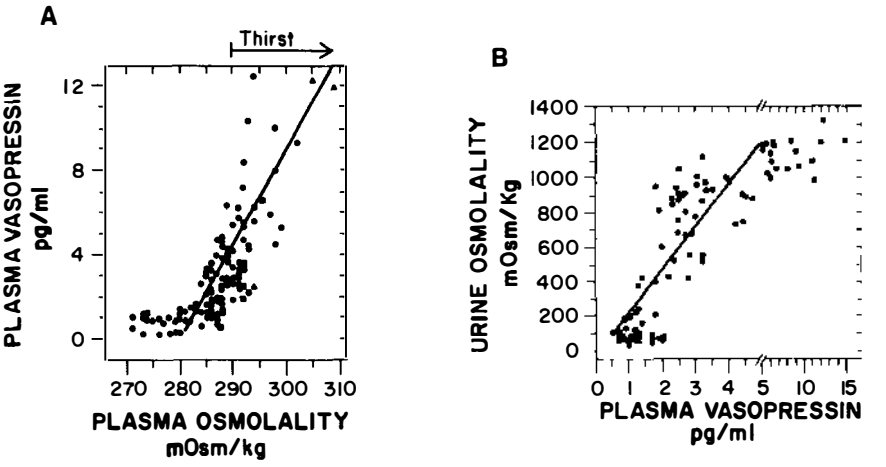

Figure 1 Relationships of plasma vasopressin to plasma osmolality *(a)* and urine osmolality *(b)* in healthy adults. The arrow indicates the level of plasma osmolality at which thirst begins. (Reprinted from 58 with permission.)

in varying states of hydration. If plasma osmolality falls below a certain point, termed osmotic threshold, plasma vasopressin is suppressed to low or undetectable levels. When plasma osmolality increases above the threshold level, plasma vasopressin rises steeply in direct proportion to osmolality. The slope of the regression line relating plasma vasopressin to osmolality defines the sensitivity of the osmoregulatory system, while the x-axis intercept provides a measure of its threshold.

The osmoregulatory system functions with remarkable precision and sensitivity. The precision can be appreciated most readily by measuring plasma vasopressin and osmolality repeatedly in the same subject during a procedure that progressively increases plasma osmolality, such as the infusion of hypertonic saline (Figure 1*a*). When such data are subjected to a regression analysis, a high degree of correlation is always observed (60). The exquisite sensitivity of the osmoregulatory system can be discerned from the fact that an increase in plasma osmolality of only 1% increases plasma vasopressin enough to effectively change the rate of water excretion by the kidney (Figure 1) (56, 58). The osmoregulatory system displays large individual differences in both the sensitivity and the threshold (51, 60). However, these differences remain relatively constant over a period as long as five years and appear to be genetically determined (56).

The osmoregulatory system is not equally sensitive to all plasma solutes. Sodium and its anions, which normally contribute more than 95% of the osmotic pressure of plasma, elicit the largest vasopressin response (95). Certain sugars, such as sucrose and mannitol, are equally effective (84, 95). In contrast, a rise in plasma osmolality produced by urea or glucose has little or no effect on vasopressin in healthy adults or animals (46, 77, 95). The basis for this osmoreceptor specificity is still unclear, but the current understanding is that the osmoreceptor is stimulated by osmotically induced changes in its water content (56, 84). According to this concept the stimulatory potency of a given solute is inversely proportional to the rate at which it moves from plasma into the osmoreceptor. Therefore, solutes that penetrate the cell readily, such as glucose and urea, do not create an osmotic gradient across the osmoreceptor and have no effect on vasopressin secretion. In contrast, obligatory extracellular solutes such as sodium and mannitol create an osmotic gradient across the osmoreceptor and stimulate vasopressin release (84, 95).

The exact mechanism by which osmolality influences the secretion of vasopressin is not clearly understood. It requires the presence of neurons collectively known as osmoreceptors (84). The location of the osmoreceptors is uncertain, but anatomical, physiological, and pathological studies indicate that it is in the anterior hypothalamus (39), probably in the area that involves the organum vasculosum laminae terminals (48). They are near but separate from the vasopressin-producing neurons since some patients with hypo-

thalamic pathology (53), as well as experimental animals with small ablative lesions in the anterior hypothalamus (48), selectively lose their vasopressin response to osmolality but still release the hormone in response to nonosmotic stimuli. The osmoreceptors appear to be located on the blood side of the blood-brain barrier because urea does not stimulate vasopressin secretion (46, 77, 95) even though it crosses the blood-brain barrier poorly.

The functional properties of the osmoregulatory system are affected by numerous factors. In fact, most of the nonosmotic stimuli that influence vasopressin release do so not by disrupting the osmoreglation but rather by altering the threshold, sensitivity, and/or solute specificity of the osmoregulatory system (56, 58, 87, 88).

Baroregulation The secretion of vasopressin can also be altered by changes in blood pressure and/or volume (51, 84). These hemodynamic changes are detected by the stretch receptors in cardiac atria, aortic arch, and carotid sinuses; from there, the signals are transmitted via vagal and glossopharyngeal nerves to the nucleus tractus solitarii in the brain stem (56, 91); and finally postsynaptic pathways that are partly noradrenergic project to the magnocellular neurons of the supraoptic and paraventricular nuclei (66). The input from the baroreceptors appears to be tonically inhibitory under normal conditions since their interuption results in an acute rise in plasma vasopressin (75). Recent studies indicate that central opioid pathways may be involved in the baroregulation since the opioid antagonist diprenorphine selectively inhibits vasopressin response to hypovolemia but has no effect on response to osmotic stimuli (59).

The functional properties of the baroregulatory system differ from those of the osmoregulatory system (23, 57). While the relationship of plasma vasopressin to osmolality appears to be linear, the relationship to hemodynamic changes is exponential. Thus, small changes in blood volume and/or pressure, on the order of 5–10%, have little or no effect on vasopressin secretion, while greater decreases of 20–30% elevate plasma vasopressin to levels many times higher than those needed for maximal antidiuresis (23). The relative insensitivity of plasma vasopressin to small hemodynamic changes means that baroregulatory mechanisms play little or no role in the normal control of water balance. Under normal circumstances, total body water rarely changes by more than 1–2%, an amount far too small to affect vasopressin secretion through nonosmotic influences.

The hemodynamic changes influence vasopressin secretion not by disrupting the osmoregulation but rather by altering the functional properties of the osmoregulatory system (57, 90). Thus, smaller changes in blood volume (10%) result in lowering of the osmotic threshold for vasopressin secretion while greater reductions in volume or pressure also cause an increase in the

sensitivity of vasopressin response to the osmolality (92). It should be noted, however, that in the presence of a hemodynamic stimulus, vasopressin continues to respond appropriately to small changes in plasma osmolality and, even more importantly, can still be fully suppressed if plasma osmolality falls below the new lower set point. The preservation of the threshold function helps to limit the water retention and hyponatremia that develop in response to hypovolemia (56).

Other influences Numerous other factors have been found to alter vasopressin secretion (Table 1) (56, 87). Among these, nausea is the most potent. Whether induced via chemoreceptor trigger zone (63) or by vestibular mechanism (27), nausea, with or without vomiting, consistently increases plasma vasopressin to levels considerably higher than those achieved with other stimuli (63). The teleological reason for such potent vasopressin response to nausea is unclear. However, this factor should always be looked for if unexpected elevations of the hormone are encountered in research studies or if osmotically inappropriate secretion of vasopressin occurs in patients who have diseases or take drugs that can induce nausea.

Hypoglycemia stimulates the release of many hormones, including vasopressin. This effect occurs both in rats (7) and in humans (8) and is proportional to the degree of hypoglycemia achieved (8). The mechanism by which hypoglycemia causes a release of vasopressin appears to be intracellular glycopenia since a similar effect can be produced by administration of 2-deoxyglucose (58, 87).

The normal menstrual cycle and pregnancy also influence the secretion of vasopressin. Dynamic studies of osmoregulation revealed lowering of the threshold for vasopressin release in the luteal phase of the normal menstrual cycle (73, 86). An even larger decrease in the threshold has been observed in both rat (24) and human pregnancy (19). The mechanism by which the luteum and pregnancy alter vasopressin secretion is unclear, but probably does not involve a decrease in "effective" plasma volume (4).

Insulin-deficient diabetes mellitus (89, 97) has been associated with increased vasopressin levels. The vasopressin elevation appears to be due to the effect of insulinopenia on the specificity of the osmoreceptor (85). Thus, in healthy humans (95) and animals (77), glucose does not stimulate vasopressin secretion because it permeates the osmoreceptor neurons freely. However, in the absence of insulin, glucose becomes osmotically effective and vasopressin is released in response to hyperglycemia (85). The finding that insulin influences the osmoreceptor function explains, at least in part, the observed vasopressin elevation in hyperglycemic diabetic patients and also suggests an important link between a hormone that is affected by feeding behavior (insulin) and one that regulates water metabolism (vasopressin).

Table 1 Factors influencing vasopressin secretion

I. Osmotic
- Plasma osmolality
  - Changes in hydration
  - Infusion of hypertonic or hypotonic solutions
  - Hyperglycemia with insulin deficiency

II. Hemodynamic
- Blood volume (total or effective)
  - Posture
  - Hemorrhage
  - Aldosterone deficiency or excess
  - Gastroenteritis
  - Congestive failure
  - Cirrhosis
  - Nephrosis
  - Positive pressure breathing
  - Diuretics
- Blood pressure
  - Orthostatic hypotension
  - Vasovagal reaction
  - Drugs (isoproterenol, norepinephrine, nicotine nitroprusside, trimethaphan, histamine, bradykinin)

III. Emetic
- Nausea
  - Drugs (apomorphine, morphine, nicotine)
  - Motion sickness

IV. Glucopenic
- Insulin-induced hypoglycemia
- 2-Deoxyglucose-induced intracellular glucopenia

V. Other
- Menstrual cycle
- Pregnancy
- Aging
- Diabetes mellitus
- Hypercalcemia
- Hypokalemia
- Stress (?)
- Temperature
- Angiotensin
- Hypoxia, hypercapnea, acidosis

VI. Drugs and hormones
- Stimulatory
  - Acetylcholine
  - Nicotine
  - Apomorphine
  - Morphine (high doses)
  - Epinephrine
  - Isoproterenol
  - Histamine
  - Bradykinin
  - Prostaglandins
  - β-Endorphin
  - Cyclophosphamide i.v.
  - Vincristine
  - Insulin
  - 2-Deoxyglucose
  - Angiotensin
  - Lithium
- Inhibitory
  - Norepinephrine
  - Fluphenazine
  - Haloperidol
  - Promethazine
  - Oxilorphan
  - Butorphanol
  - Morphine (low doses)
  - Alcohol
  - Carbamazepine
  - Glucocorticoids
  - Phenytoin (?)
  - Fentanyl anesthesia

Numerous other physiological and pathological conditions as well as many drugs can also influence vasopressin secretion (Table 1). Even though they have little significance for normal water balance, they may be responsible for spurious results of research studies and for clinically significant alterations of fluid and electrolyte balance, such as iatrogenic hyponatremia.

VASOPRESSIN ACTION The most important biological action of vasopressin is to conserve body water by reducing the rate of urine output (56). The antidiuretic effect is achieved by promoting the reabsorption of solute-free water in the distal and collecting tubules of the kidney, which results in an increase in urine concentration and a decrease in urine flow (10). In healthy adults, the stimulus response relationship between plasma vasopressin and urine concentration is extremely sensitive (Figure 1*b*): the full range of urinary concentrations and dilution can be achieved by changing the plasma vasopressin concentration between 0.5 and 5 pg/ml (Figure 2) (60).

The effect of vasopressin on urine concentration and flow is markedly influenced by changes in the volume of the filtrate presented to the distal tubule. When proximal reabsorption is reduced by volume expansion or the presence of unreabsorbable solutes such as mannitol, considerably more than 15% of the filtrate may escape and overwhelm the limited capability of the

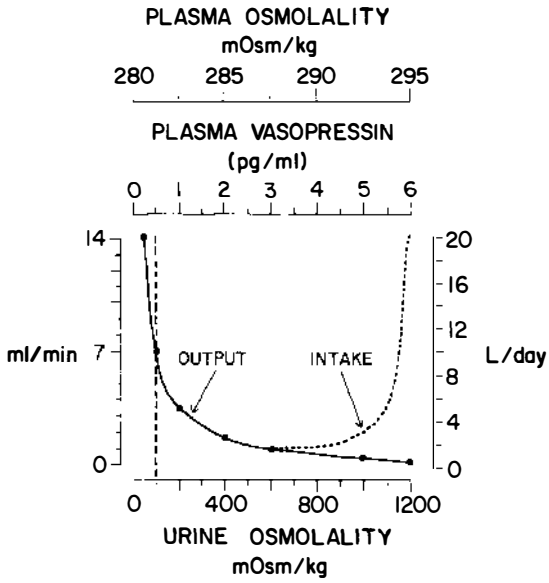

Figure 2 Relationships between plasma osmolality, plasma vasopressin, urine osmolality, and water intake or output in a healthy adult. An average solute excretion rate of 600 mosmol/day and an insensible loss of 1 liter/day were assumed. (Redrawn from 58 with permission.)

distal tubule to reabsorb water. As a consequence, the urine osmolality falls and the flow rises even in the presence of supramaximal levels of vasopressin (56, 58, 88). Conversely, in clinical situations in which the actual or effective blood volume is reduced (such as congestive heart failure or cirrhosis), the proximal nephron reabsorbs an increased proportion of the glomerular filtrate. When the distal tubule is presented with a reduced amount of concentrated filtrate, the ensuing urine will have low volume and increased osmolality even in the absence of vasopressin. In addition, the antidiuretic effect of vasopressin may also be inhibited by a decrease in the medullary gradient, which is most often caused by chronic water diuresis. Polyuria of any etiology causes a "medullary washout" that prevents maximal increase in urine concentration even in the presence of vasopressin levels many times higher than those required for maximal antidiuresis (56, 94).

Thirst

In addition to antidiuretic hormone, thirst also plays a very important role in maintaining water homeostasis. Thirst is defined as a conscious desire to drink and must be differentiated from drinking itself, which may occur for reasons other than thirst. In fact, most drinking under conditions of daily living is not induced by thirst, but rather motivated by social customs or associated with meals. The function of the thirst mechanism is to ensure that water will be replenished promptly when a deficiency occurs.

Scientific studies of thirst are hampered by the inability to measure it directly or to quantitate it precisely. Nevertheless, it is clear that thirst is stimulated by many of the same factors that influence vasopressin secretion (55). As for vasopressin, the principal stimulus for thirst is an increase in the extracellular fluid or plasma osmolality. The sensitivity of thirst to changes in plasma osmolality is illustrated by the fact that an increase in osmolality of only 2–3% above the basal levels produces a strong desire to drink (31, 34). The absolute level of plasma osmolality at which thirst is first perceived is termed the osmotic threshold for thirst. Even though there is a wide individual variability in the thirst threshold among healthy people, the average value of 295 mosmol/kg is considerably higher than the osmotic threshold for vasopressin release (around 280 mosmol/kg).

The mechanism by which increased plasma osmolality stimulates thirst is unclear. It probably involves osmoreceptor neurons located in the anterior hypothalamus (48), near but probably separate from osmoreceptors for vasopressin release (2, 38).

The solute specificity of thirst appears to be similar to that described for vasopressin. Thus, sodium and mannitol stimulate thirst while urea does not (95). The only exception is glucose, which does not stimulate vasopressin in healthy adults or animals (46, 77, 95) but seems to be a weak dipsogen when

studied carefully in humans (T. Vokes and G. L. Robertson, unpublished observations).

Similarly to vasopressin, thirst is also stimulated by a reduction in plasma volume (30). Experimentally, hypovolemic thirst has been produced by graded hemorrhage, sodium depletion, extravascular sequestration of extracellular fluids, or obstruction of the venous return to the heart (31). The magnitude of the reduction in circulating volume necessary to stimulate thirst is similar if not larger than that needed to stimulate vasopressin release and is on the order of 10–15%.

The mechanisms by which hypovolemia produces thirst are probably similar to those that mediate vasopressin secretion and involve the stretch receptor of the heart and large blood vessels and their vagal efferents (78). In addition, the effect of hypovolemia on thirst may also be mediated by the renin-angiotensin system (31). In experimental animals, angiotensin is a potent dipsogen when administered systemically (33) or intracerebroventricularly (26, 32). In humans, however, the evidence is less clear. Even though occasional patients with hyperreninemia have been reported to have uncontrollable thirst (17, 62), most patients with high levels of renin and angiotensin have no apparent abnormality of water intake (17, 55). These observations suggest that, at least in man, angiotensin does not play a major role in the regulation of thirst.

Other factors that influence thirst include the luteal phase of the normal menstrual cycle and pregnancy, both of which lower the thirst threshold as well as the osmotic threshold for vasopressin release (3, 19, 24, 73, 86). Hypokalemia and hypercalcemia also stimulate thirst (9, 31), which probably contributes to the polyuria observed in both of these disorders (9).

Another aspect of thirst regulation that deserves attention is satiety. It has been shown that dehydrated dogs correctly replace the fluid deficit within 5 minutes (79) and that anephric rats infused with hypertonic saline ingest the amount of water needed to restore plasma osmolality to the basal level (29). Even though little is known about the mechanism by which thirst osmoreceptors influence drinking behavior, some information is available about the anatomic origin of satiety signals. Thrasher et al (79) showed that in dehydrated dogs oropharingeal signals mediate short-term satiety, which causes the animal to stop drinking before water is absorbed and plasma osmolality corrected. In contrast, the long-term satiety probably involves the hypothalamic osmoreceptor since it requires restoration of plasma osmolality (79).

Maintenance of Salt and Water Balance

As mentioned previously, thirst and antidiuretic hormone, vasopressin, play a key role in maintaining water balance—primarily by keeping the osmolality

of plasma and extracellular fluid in a remarkably narrow range (56, 58, 88). In each individual, the lower limit of this range is determined by the osmotic threshold for vasopressin release, while the upper limit is determined by the osmotic thirst threshold. If excess water is ingested, plasma osmolality falls below the threshold for vasopressin release, and plasma levels of the hormone decrease to undetectably low values. As a consequence, urine osmolality falls while urine flow increases. This leads to a prompt excretion of solute-free water and restoration of plasma osmolality to the previous level. Conversely, if water is lost in excess of sodium, plasma osmolality increases. This stimulates secretion of vasopressin, which promotes antidiuresis and water conservation. Provided the access to water is unrestricted, a rise in plasma osmolality above the threshold for thirst will also increase the water intake, which will dilute the body fluids to the previous level.

PATHOLOGY

Vasopressin Deficiency

Deficient secretion or action of the antidiuretic hormone vasopressin manifests as polyuria (daily urine output >30 ml/kg). In clinical practice, the most common cause of polyuria is diabetes mellitus, in which increased urine output is due to glucosuria. This and other forms of solute diuresis can be identified by testing urine for sugar or calculating total daily solute excretion. If the latter is above 1500 mosmol/kg, the polyuria is probably due to solute diuresis. If solute excretion is below 1500 mosmol/kg and the urine is dilute (less than 250 mosmol/kg), polyuria is due to water diuresis and is referred to as diabetes insipidus. The latter can result from one of three defects: (*a*) decreased or absent production of vasopressin, referred to as central, cranial, or neurogenic diabetes insipidus; (*b*) suppression of vasopressin secretion by high fluid intake, termed dipsogenic diabetes insipidus or primary polydipsia; and (*c*) decreased or absent renal response to vasopressin, known as nephrogenic or vasopressin-resistant diabetes insipidus (56, 58, 88).

All three forms of diabetes insipidus have diverse and multiple etiologies (Table 2). Neurogenic diabetes insipidus may be idiopathic or result from an identifiable pathological process involving the hypothalamus and or the neurohypopysis (56, 88). Nearly any neoplastic, vascular, granulomatous, or infectious disease of the hypothalamus can destroy the vasopressin-producing cells and cause the hormone deficiency. Pathological processes restricted to the pituitary cause vasopressin deficiency by destroying the neurohypophysis or interrupting the stalk that leads to the retrograde degeneration of the neurosecretory cells (45, 49). However, since many axons terminate proximally, in the stalk or the infundibulum, the interruption of the neurohypophysis must be at or above that level to reduce the secretory capacity by

85%, the minimum required to produce clinically significant polyuria (56, 58). The anatomic basis for vasopressin deficiency in patients with idiopathic forms of diabetes insipidus is the atrophy of the neurohypophysis and hypocellularity of the supraoptic and paraventricular nuclei (13, 16). The pathological mechanism that leads to the destruction of the vasopressinergic cells remains unclear. A proportion of patients with idiopathic diabetes insipidus have a familial form of the disease that is similar to other idiopathic cases both in the clinical presentation and pathological findings (56). The pattern of inheritance is autosomal dominant but the molecular basis of the genetic defect responsible for the disease has not been identified.

The primary polydipsia is either caused by pathological processes of the hypothalamus leading to abnormal thirst stimulation (74) or else is associated with psychoses wherein the high rate of water intake is apparently induced not by thirst but by psychotic ideation (54).

Table 2 Causes of diabetes insipidus

I.	Vasopressin deficiency (neurogenic diabetes insipidus)
	Acquired
	Trauma (accidental, surgical)
	Tumors (craniopharyngioma, metastases, lymphoma)
	Granuloma (sarcoid, histiocytosis, tuberculosis, syphilis)
	Infectious (meningitis, encephalitis, Guillain-Barré syndrome)
	Vascular (Sheehan's syndrome, aneurysms, aortocoronary bypass, cerebral thrombosis)
	Idiopathic
	Familial (autosomal dominant)
II.	Excessive water intake (primary polydipsia)
	Granuloma (neurosarcoid)
	Psychogenic
	Idiopathic (resetting of the osmostat)
III.	Vasopressin insensitivity (nephrogenic diabetes insipidus)
	Acquired
	Infectious (pyelonephritis)
	Postobstructive (prostatic, ureteral)
	Vascular (sickle cell disease, trait)
	Infiltrative (amyloid)
	Cystic (polycystic disease)
	Metabolic (hypokalemia, hypercalcemia)
	Granuloma (sarcoid)
	Toxic (lithium, demeclocycline, methoxyflurane)
	Solute overload (glucosuria)
	Familial (X-linked recessive)

Nephrogenic diabetes insipidus can be a familial disorder inherited as an X-linked recessive trait (93), or is secondary to various pathological processes and drugs that affect the kidney (71) (Table 2).

The pathophysiology of diabetes insipidus differs depending on the type. In neurogenic diabetes insipidus, the primary defect is a deficient secretion of vasopressin that leads to increased urinary losses of solute-free water, which in turn increases plasma osmolality and stimulates thirst. The resultant increase in water intake compensates for the high rate of output and prevents further dehydration. The net effect is the high rate of urine output (polyuria) and fluid intake (polydipsia), while plasma osmolality stabilizes at a somewhat higher level, approximating the osmotic threshold for thirst (56, 58). In patients with nephrogenic diabetes insipidus, the pathophysiology is similar but the pathogenetic mechanism is an absent or deficient renal response to vasopressin that is secreted in normal or even increased amounts (56, 94).

In patients with primary polydipsia, the initial event is increased water intake, which lowers plasma osmolality and suppresses vasopressin. As a consequence, urine osmolality also falls and urine volume increases. As in other forms of diabetes insipidus, the end result is a high rate of fluid intake and urine output. The difference is, however, that the plasma osmolality stabilizes at a lower level, near or slightly below the level of osmotic threshold for vasopressin release. Only if water intake is extremely high (over 25 liters per day) will the excretory capacity of the kidney be surpassed, resulting in dilutional hyponatremia in the absence of abnormalities in vasopressin secretion (56).

Thirst Deficiency

If fluid intake is not sufficient to match renal and extrarenal losses, hypernatremia and hyperosmolality of body fluids will invariably develop. In a patient who has a free access to water and no neurological impairments, hypernatremia always indicates some intrinsic defect in the osmoregulation of thirst. Conversely, if thirst is normal, hypernatremia will not develop even if vasopressin is deficient and/or fluid loss very high (55). This is exemplified by patients with neurogenic or nephrogenic diabetes insipidus who maintain plasma sodium and osmolality in the normal range even in the face of extremely high urinary losses.

Chronic hypernatremia with deficient thirst is observed with a variety of intracranial pathology, usually localized in or around the hypothalamus. The conditions that have been described in association with this disorder include vascular, neoplastic, and granulomatous diseases of the hypothalamus as well as hydrocephalus, trauma, and a few apparently idiopathic cases (38, 53).

Most patients with deficient thirst also have abnormal vasopressin response to osmotic stimuli, which indicates that the osmoreceptors for thirst and

vasopressin secretion are anatomically very close (20, 21, 37, 53, 67). Since neurohypophysis is usually intact, the response of vasopressin to nonosmotic stimuli such as hypovolemia, hypotension, nausea, or hypoglycemia is normal (20, 37), a finding that differentiates these patients from those with true neurogenic diabetes insipidus in whom vasopressin responds subnormally to most if not all stimuli (6). Recently, however, Hammond et al (38) described a patient with absent thirst but normal osmoregulation of vasopressin suggestive of a selective destruction of the thirst osmoreceptor or its efferent pathways.

Excessive Vasopressin Secretion and Thirst

Excessive thirst and water intake in the face of normal vasopressin secretion manifest as primary polydipsia or dipsogenic diabetes insipidus. However, excessive thirst coupled with excessive osmotically inappropriate vasopressin secretion leads to water retention and dilution of body fluids resulting in hypoosmolemia and hyponatremia.

Hyponatremic disorders are usually divided into three categories—hypervolemic, hypovolemic, and euvolemic—depending on whether the total body sodium and extracellular fluid volume are increased, decreased, or normal. In hypervolemic and hypovolemic forms, the hypersecretion of vasopressin, although inappropriate for the concurrent hypoosmolality of body fluids, is a normal physiological response to a decrease in total and/or effective blood volume. In contrast, in the euvolemic hyponatremia, referred to as Schwartz-Barther syndrome or syndrome of inappropriate antidiuretic hormone secretion (SIADH), the hypersecretion of vasopressin cannot be attributed to recognized osmotic or volemic stimuli. All three forms are characterized by hyponatremia associated with impaired water excretion. However, the etiology, pathogenesis, and clinical features are quite different in each form.

HYPERVOLEMIC HYPONATREMIA Hypervolemic hyponatremia is observed in conditions associated with generalized edema such as congestive heart failure (72, 76), cirrhosis (11, 72), and occasionally in nephrotic syndrome (81). The clinical presentation of hypervolemic hyponatremia is characterized by the combination of generalized edema and signs of decreased intravascular volume such as tachycardia, orthostatic hypotension, prerenal azotemia, increased plasma renin and aldosterone, and decreased urinary sodium. Salt and water are retained despite a significant increase in total body sodium, probably because of a decrease in the "effective plasma volume."

The mechanism by which effective hypovolemia leads to hyponatremia involves a reduction in the glomerular filtration rate and an increase in the proximal tubular reabsorption of filtered electrolytes and water. As a conse-

quence, less filtrate is delivered to the diluting segment of the nephron and the ability to excrete free water is diminished. Water retention is further aggravated by increased reabsorption of free water in the distal and collecting ducts, an increase due to increased secretion of vasopressin (11, 76, 81). Studies of vasopressin function indicate that the elevated hormone levels are caused by a downward resetting of the osmostat (80), probably as a consequence of effective hypovolemia.

HYPOVOLEMIC HYPONATREMIA Hypovolemic hyponatremia is seen in conditions in which total body sodium and extracellular fluid volume are decreased (56, 58). The clinical presentation is characterized by signs of decreased intravascular volume such as tachycardia, orthostatic hypotension, and prerenal azotemia. Urinary sodium is typically low except when the hypovolemia is due to renal sodium wasting as are some forms of renal disease, mineralocorticoid deficiency, and diuretic use or abuse. Diuretics induce hyponatremia by several mechanisms (1, 28). Firstly, thiazides inhibit sodium reabsorption in the diluting segments of the nephron. Consequently, maximal urinary dilution is impaired and the retention of free water promoted. In addition, the diuretics induce a contraction of the extracellular fluid volume, which in turn decreases the glomerular filtration and increases proximal reabsorption of salt and water. Finally, vasopressin secretion can also be stimulated by hypovolemia, thereby contributing to water retention (28, 92).

A deficiency of mineralocorticoid and/or glucocorticoid hormones has also been associated with hyponatremia (68). In isolated mineralocorticoid deficiency, sodium wasting produces hypovolemia, which leads to hyponatremia through reduction in glomerular filtration rate, increased proximal reabsorption, and a decreased distal delivery as well as through a stimulation of vasopressin secretion (15). The mechanism by which pure glucocorticoid deficiency produces hyponatremia is less clear because this condition is not associated with easily demonstrable hypovolemia. The impaired water excretion is believed to be due to the effect of decreased cardiac output on renal hemodynamics as well as on vasopressin secretion (44).

Hypovolemic hyponatremia can also be observed in diarrhea, bulimia, renal tubular acidosis, and other conditions that cause sodium depletion (56).

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH) The euvolemic hyponatremia of this syndrome is characterized by normal or only slightly increased blood volume and pressure and by absence of edema. The clinical manifestations are those of hyponatremia.

SIADH has been observed in many different clinical situations (Table 3). Most are associated with malignant tumors, diseases of the lung and central

nervous system, or administration of certain medications. The basic abnormality in SIADH is persistent vasopressin secretion in the face of hypoosmolality and hyponatremia. By definition, hypovolemia and other nonosmotic stimuli for vasopressin secretion are absent, as are renal, adrenal, and thyroid deficiency (5). In SIADH, vasopressin can be secreted ectopically by malignant or granulomatous tissue or eutopically by the neurohypophysis (52, 96). The plasma levels of vasopressin, although high for the concurrent hypoosmolality of body fluids, are usually not high in absolute terms since they are in the range found in normally hydrated healthy adults (52, 56, 96).

Table 3 Disorders associated with SIADH

I.	Malignant tumors	III.	Diseases of the lung
	Carcinoma of the lung		Pneumonia
	Carcinoma of the duodenum		Tuberculosis
	Carcinoma of the pancreas		Cavitation
	Thymoma		Empyema
	Mesothelioma		Cystic fibrosis
	Carcinoma of the bladder		Pneumothorax
	Carcinoma of the ureter		Asthma
	Prostatic carcinoma		Positive-pressure breathing
	Lymphoma		
	Ewing's sarcoma	IV.	Drugs
			Vasopressin and DDAVP
II.	Disorders of the CNS		Oxytocin
	Meningitis		Clofibrate
	Encephalitis		Chlorpropamide
	Brain abscess		Thiazide diuretics
	Guillain-Barré syndrome		Phenothiazines
	Head trauma		MAO inhibitors
	Subarachnoid hemorrhage		Tricyclic antidepressants
	Cerebrovascular accident		Carbamazepine
	Cavernous sinus thrombosis		Nicotine
	Brain tumors		Vincristine, vinblastine
	Olfactory neuroblastoma		Cisplatin
	Cerebellar and cerebral atrophy		
	Hypoplasia of corpus callosum	V.	Acute psychosis
	Hydrocephalus		
	Neonatal hypoxia		
	Multiple sclerosis	VI.	Postoperative period
	Delirium tremens		
	Wernicke's encephalopathy		
	Shy-Drager syndrome	VII.	Endocrine diseases
	Acute intermittent porphyria		Myxedema (rarely)
	Rocky Mountain spotted fever		Adrenal insufficiency
	Tetanus		
		VIII.	"Idiopathic"

Consequently, hypersecretion can be identified with certainty only by relating vasopressin levels to plasma osmolality or sodium under conditions of hypoosmolality. In a minority of patients, however, vasopressin secretion is completely normal but urine osmolality remains inappropriately elevated in the face of hypoosmolality and in the absence of detectable vasopressin (41, 52, 96). In these patients, urinary concentration may be due to a yet unidentified antidiuretic substance or to increased renal sensitivity to subthreshold levels of vasopressin.

The pathogenesis of hyponatremia in SIADH is similar to that produced by administration of vasopressin to healthy volunteers (43). If water intake is normal, i.e. 1 to 2 liters a day for an adult, producing fixed antidiuresis has little or no effect on body water and sodium content. However, if fluid intake increases even slightly, a compensatory rise in urinary water excretion cannot occur because plasma vasopressin cannot be suppressed and urine cannot be diluted in response to hyponatremia. Consequently, a portion of ingested water is retained every day and may accumulate sufficiently to cause a progressive expansion of body fluids and dilutional hyponatremia. When body fluids are expanded more than 10%, the urinary excretion of sodium increases primarily because of decreased reabsorption in the proximal tubule. This natriuresis partially corrects the hypervolemia and prevents the occurrence of edema or hypertension but further aggrevates hyponatremia. Therefore, the severity of hyponatremia depends primarily on the rate of water intake rather than on the level of antidiuresis or plasma vasopressin. For the same reason, water restriction is a very effective measure for treating the hyponatremia of SIADH.

The pathophysiology is slightly different in a subset of patients that have a variant of SIADH known as reset osmostat (52, 96). In this subset, plasma vasopressin and urinary concentration can be maximally suppressed if plasma osmolality and sodium are sufficiently lowered, usually to the levels considerably below normal. Therefore, the severity of hyponatremia in these patients is determined not only by the rate of water intake but also by the new level of the osmotic threshold for vasopressin release.

NUTRITION AND WATER BALANCE

Changes in water balance have been observed in conditions associated with altered food intake and/or body weight. Obesity has been associated with a tendency to retain salt and water and with abnormalities in the regulation of vasopressin secretion (22). The latter was observed when the response of obese subjects to salt and water loading was studied during baseline obesity, after 37 days of fasting, and after 37 days of hypocaloric (1000 calories/day) refeeding (22). In the baseline obese state, the response to water loading was

abnormal since plasma vasopressin did not decrease to the levels observed in normal subjects. As a consequence, the obese patients failed to dilute urine appropriately and excreted a significantly smaller percentage of the water load in 4 hours than did the lean controls (65 ± 12% in obese vs 98–137% in controls). The response of vasopressin to salt loading was also abnormal in the baseline obese state since the infusion of hypertonic saline produced erratic hormone levels that did not correlate with plasma osmolality. This is markedly different from the response in healthy adults, who invariably display a strong positive correlation between the two variables.

In the same study, the abnormal vasopressin response to salt and water loading was partially corrected by fasting and hypocaloric refeeding. During fasting, water loading resulted in normal suppression of plasma vasopressin levels. Despite that, however, the percentage of water load excreted in 4 hours (46 ± 9%) was subnormal, probably because of a reduction in solute diuresis, which is essential for normal urinary dilution and generation of free water. During hypocaloric refeeding, plasma vasopressin response to water loading was normal and the percentage of water excreted in 4 hours (70 ± 18%) closer to, but still lower than, that in controls. The response to salt loading showed an improvement after fasting, as well as during the hypocaloric refeeding. In both studies, the increase in plasma osmolality, (produced by the infusion of hypertonic saline) resulted in an appropriate rise in plasma vasopressin. However, the slope of the line relating plasma vasopressin to osmolality (a measure of the sensitivity of osmoregulatory response) was lower during fasting (0.12) than in the same subjects studied after refeeding (0.28) or in normal controls (0.31).

These results suggest that obesity causes an abnormality in the hypothalamic control of vasopressin secretion that can be corrected, at least in part, by caloric reduction and weight loss. The mechanisms by which changes in nutrition exert influence on the hypothalamic function are unclear. One possibility is that some of the effects are mediated by changes in the circulating insulin levels, which have been shown to influence the osmoregulation of vasopressin at least in patients with diabetes mellitus (85). Even though the pathophysiological consequences of vasopressin abnormalities observed in obesity are not completely clear, it is conceivable that the water-retaining tendency of obese subjects could be caused partly by a failure to suppress vasopressin by hypoosmolality normally.

Abnormalities in vasopressin regulation have been observed on the opposite end of nutritional spectum, i.e. in anorexia nervosa (35), a psychiatric syndrome characterized by a marked reduction in food intake in the obsessive pursuit of thinness. Earlier studies have reported defects in urinary concentration and dilution (47). More recently the nature of vasopressin abnormalities was studied by examining the hormone response to osmotic stimulation in

anorexic patients in the underweight state, during short-term recovery, and after full recovery (35). In the underweight state, all patients had an abnormal vasopressin response to increasing plasma sodium—in one patient the response was subnormal, while in the other three it was erratic and resulted in plasma vasopressin levels that were not significantly correlated with sodium. In subjects studied after short-term recovery, vasopressin response improved, i.e. the plasma levels of the hormone were correlated with sodium levels. However, the absolute levels of vasopressin remained lower than in the controls. Finally, after full recovery, the response of vasopressin to osmolality was completely normal.

These results indicate that the nutritional abnormality and/or psychiatric disturbance of anorexia nervosa influence the hypothalamic regulation of vasopressin. The mechanism of such influence is presently unclear but does not appear to involve any of the recognized nonosmotic stimuli for vasopressin secretion. The pathophysiological consequences of abnormal vasopressin regulation are not clear either. None of the patients had gross abnormalities in systemic water balance as evidenced by normal plasma concentrations of sodium. However, subnormal vasopressin response to increasing plasma sodium could be responsible, at least in part, for the increased urine output frequently observed in patients with anorexia nervosa.

Profound changes in the water and electrolyte balance have also been observed during fasting and refeeding. Initial days of fasting are accompanied by a marked increase in the renal excretion of sodium (12, 14). Prolonged fasting, however, leads to sodium conservation while refeeding, particularly with carbohydrates, causes an avid sodium retention (14, 83). The mechanisms by which fasting and refeeding alter the excretion of sodium are a subject of debate. Possible explanations include the obligatory cation coverage of metabolically generated organic acids (69), elevation of circulating glucagon (42, 65), and suppression of insulin (40). Regardless of the mechanism, however, the natriuresis of fasting is responsible for the large proportion of the weight loss that occurs in the first week of fasting (12, 14).

The mechanism by which alterations in urinary sodium excretion cause marked changes in body weight is as follows: During fasting, the urinary sodium loss leads to a decrease in plasma sodium and osmolality and thereby inhibits vasopressin secretion. As a result, urinary excretion of water increases, which leads to a significant reduction in total body water and a decrease in body weight. Conversely, during refeeding, sodium retention leads to an increase in plasma sodium and thirst and to a stimulation of vasopressin secretion. The resultant increase in water intake and decrease in renal water excretion increase the total body water and augment the body weight. These changes in sodium and water balance fully explain the observation that the weight loss in the first week of fasting and the weight gain in the

initial phases of refeeding are far greater than could be predicted from the changes in the caloric balance.

The above-described alterations in vasopressin secretion and water balance observed during dietary modifications, in obesity and in anorexia nervosa, are examples of an important link between the regulation of nutrient metabolism and water homeostasis. Further studies are needed to uncover the mechanisms by which nutrition influences the regulation of water and electrolyte balance in health and disease.

Literature Cited

1. Abramow, M., Cogan, E. 1984. Clinical aspects and pathophysiology of diuretic-induced hyponatremia. In *Adv. Nephrol.* 13:1–27
2. Andersson, B., Olsson, K., Warner, R. G. 1967. Dissimilarities between the central control of thirst and the release of antidiuretic hormone (ADH). *Acta Physiol. Scand.* 71:57–64
3. Barron, W. M., Durr, J., Stamoutsos, B. A., Lindheimer, M. D. 1985. Osmoregulation and vasopressin secretion during pregnancy in Brattleboro rats. *Am. J. Physiol.* 248(17):R29–37
4. Barron, W. M., Stamoutsos, B. A., Lindheimer, M. D. 1984. Role of volume in the regulation of vasopressin secretion during pregnancy in the rat. *J. Clin. Invest.* 73:923–32
5. Bartter, F. C. 1973. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *Dis. Mon.*, November
6. Baylis, P. H., Gaskill, M. B., Robertson, G. L. 1981. Vasopressin secretion in primary polydipsia and cranial diabetes insipidus. *Q. J. Med.* 50:345–58
7. Baylis, P. H., Robertson, G. L. 1980. Rat vasopressin response to insulin-induced hypoglycemia. *Endocrinology* 107:1975–79
8. Baylis, P. H., Zerbe, R. L., Robertson, G. L. 1981. Arginine vasopressin response to insulin-induced hypoglycemia in man. *J. Clin. Endocrinol. Metab.* 53:935–40
9. Berl, T., Linas, S. L., Aisenbrey, G. A., Anderson, R. J. 1977. On the mechanism of polyuria in potassium depletion. *J. Clin. Invest.* 60:620–25
10. Berliner, B. W., Levinsky, N. G., Davidson, D. G., Eden, M. 1958. Dilution and concentration of the urine and the action of antidiuretic hormone. *Am. J. Med.* 24:730–44
11. Bichet, D., Szatalowicz, V., Chaimovitz, C., Schrier, R. W. 1982. Role of vasopressin in abnormal water excretion in cirrhotic patients. *Ann. Intern. Med.* 96:413–17
12. Bloom, W. L., Mitchell, W. Jr. 1960. Salt excretion of fasting patients. *Arch. Intern. Med.* 106:321–26
13. Blotner, H. 1958. Primary or idiopathic diabetes insipidus. A system disease. *Metabolism* 7:191–200
14. Boulter, P. R., Hoffman, R. S., Arky, R. A. 1973. Pattern of sodium excretion accompanying starvation. *Metabolism* 22(5):675–83
15. Boykin, J., McCool, A., Robertson, G., McDonald, K., Schrier, R. 1979. Mechanisms of impaired water excretion in mineralocorticoid-deficient dogs. *Mineral Electrolyte Metab.* 2:310–15
16. Braverman, L. E., Mancini, J. P., McGoldrick, D. M. 1965. Hereditary idiopathic diabetes insipidus: A case report with autopsy findings. *Ann. Intern. Med.* 63(3):503–8
17. Conn, J. W., Cohen, E. L., Lucas, C. P., McDonald, W. J., Mayor, G. H., et al. 1972. Primary reninism. Hypertension, hyperreninemia, and secondary aldosteronism due to renin-producing juxtaglomerular cell tumors. *Arch. Intern. Med.* 130:682–96
18. Conway, E. J., McCormack, J. I. 1953. The total intracellular concentration of mammalian tissues compared with that of the extracellular fluid. *J. Physiol.* 120:1–14
19. Davison, J. M., Gilmore, E. A., Durr, J., Robertson, G. L., Lindheimer, M. D. 1984. Altered osmotic threshold for vasopressin secretion and thirst in human pregnancy. *Am. J. Physiol.* 246(15):F105–9
20. DeRubertis, F. R., Michelis, M. F., Beck, N., Field, J. B., Davis, B. B. 1971. "Essential" hypernatremia due to ineffective osmotic and intact volume regulation of vasopressin secretion. *J. Clin. Invest.* 50:97–111

21. DeRubertis, F. R., Michelis, M. F., Davis, B. B. 1974. "Essential" hypernatremia report of three cases and review of the literature. *Arch. Intern. Med.* 134:889–95
22. Drenick, E. J., Carlson, H. E., Robertson, G. L., Hershman, J. M. 1977. The role of vasopressin and prolactin in abnormal salt and water metabolism of obese patients before and after fasting and during refeeding. *Metabolism* 26(3):309–17
23. Dunn, F. L., Brennan, T. J., Nelson, A. E., Robertson, G. L. 1973. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. *J. Clin. Invest.* 52:3212–19
24. Durr, J. A., Stamoutsos, B., Lindheimer, M. D. 1981. Osmoregulation during pregnancy in the rat. Evidence for resetting of the threshold for vasopressin secretion during gestation. *J. Clin. Invest.* 68:337–46
25. Edelman, I. S., Leibman, J. 1959. Anatomy of body water and electrolytes. *Am. J. Med.* 27:256–77
26. Epstein, A. N., Fitzsimons, J. T., Rolls, B. J. 1970. Drinking induced by injection of angiotensin into the brain of the rat. *J. Physiol.* 210:457–74
27. Eversmann, T., Guttsman, M., Uhlich, E., Ulbrecht, G., Von Werder, K., Scriba, P. C. 1978. Increased secretion of growth hormone, prolactin, antidiuretic hormone and cortisol induced by the stress of motion sickness. *Aviat. Space Environ. Med.*, Jan., pp. 53–57
28. Fichman, M. P., Vorherr, H., Kleeman, C. R., Telfer, N. 1971. Diuretic-induced hyponatremia. *Ann. Intern. Med.* 75:853–63
29. Fitzsimons, J. T. 1961. Drinking by nephrectomized rats injected with various substances. *J. Physiol.* 155:563–79
30. Fitzsimons, J. T. 1972. Thirst. *Physiol. Rev.* 52(2):468–560
31. Fitzsimons, J. T. 1985. Physiology and pathology of thirst and sodium appetite. In *The Kidney: Physiology and Pathophysiology*, ed. D. W. Seldin, G. Giebisch, pp. 885–901. New York: Raven
32. Fitzsimons, J. T., Kucharczyk, J. 1978. Drinking and haemodynamic changes induced in the dog by intracranial injection of components of the renin-angiotensin system. *J. Physiol.* 276:419–34
33. Fitzsimons, J. T., Simons, B. J. 1969. The effect on drinking in the rat of intravenous infusion of angiotensin, given alone or in combination with other stimuli of thirst. *J. Physiol.* 203:45–57
34. Gilman, A. 1937. The relation between blood osmotic pressure, fluid distribution and voluntary water intake. *Am. J. Physiol.* 120:323–28
35. Gold, P. W., Kaye, W., Robertson, G. L., Ebert, M. 1983. Abnormalities in plasma and cerebrospinal-fluid arginine vasopressin in patients with anorexia nervosa. *N. Engl. J. Med.* 308:1117–23
36. Guyton, A. C. 1986. Partition of the body fluids: Osmotic equilbria between extracellular and intracellular fluids. In *Textbook of Medical Physiology*, ed. A. C. Guyton, pp. 382–92. Philadelphia: Saunders. 7th ed.
37. Halter, J. B., Goldberg, A. P., Robertson, G. L., Porte, D. Jr. 1977. Selective osmoreceptor dysfunction in the syndrome of chronic hypernatremia. *J. Clin. Endocrinol. Metab.* 44:609–16
38. Hammond, D. N., Moll, G. W., Robertson, G. L., Chelmicka-Schorr, E. 1986. Hypodipsic hypernatremia with normal osmoregulation of vasopressin. *N. Engl. J. Med.* 14(7):433–36
39. Jewell, P. A., Verney, E. B. 1957. An experimental attempt to determine the site of the neurohypophyseal osmoreceptors in the dog. *Philos. Trans. R. Soc. London Ser. B* 240:197–324.
40. Katz, A. I., Lindheimer, M. D. 1977. Actions of hormones on the kidney. *Ann. Rev. Physiol.* 39:97–134
41. Kern, P. A., Robbins, R. J., Bichet, D., Berl, T., Verbalis, J. G. 1986. Syndrome of inappropriate antidiuresis in the absence of arginine vasopressin. *J. Clin. Endocrinol. Metab.* 62:148–52
42. Kolanowski, J., Salvador, G., Desmecht, P., Henquin, J. C., Crabbe, J. 1977. Influence of glucagon on natriuresis and glucose-induced sodium retention in the fasting obese subjects. *Eur. J. Clin. Invest.* 7:167–75
43. Leaf, A., Bartter, F. C., Santos, R. F., Wrong, O. 1953. Evidence in man that urinary electrolyte loss induced by pitressin is a function of water retention. *J. Clin. Invest.* 32:868–78
44. Linas, S. L., Berl, T., Robertson, G. L., Aisenbrey, G. A., Schrier, R. W., Anderson, R. J. 1980. Role of vasopressin in the impaired water excretion of glucocorticoid deficiency. *Kidney Int.* 18:58–67
45. Maccubbin, D. A., Van Buren, J. M. 1963. A quantitative evaluation of hypothalamic degeneration and its relation to diabetes insipidus following interruption of the human hypophyseal stalk. *Brain* 86:443–64

46. McKinley, M. J., Denton, D. A., Weisinger, R. S. 1978. Sensors of antidiuresis and thirst: Osmoreceptors or CSF sodium detectors? *Brain Res.* 141:89–103
47. Meckenburg, R. S., Loriaux, D. L., Thompson, R. H., Andersen, A. E., Lipsett, M. B. 1974. Hypothalamic dysfunction in patients with anorexia nervosa. *Medicine* 53:147–59
48. Ramsay, D. J., Thrasher, T. N., Keil, L. C. 1983. The organum vasculosum laminae terminals: A critical area for osmoreception. *Prog. Brain Res.* 60:91–98
49. Randall, R. V., Clark, E. C., Dodge, H. W. Jr., Love, J. G. 1960. Polyuria after operation for tumors in the region of the hypophysis and hypothalamus. *J. Clin. Endocrinol. Metab.* 20:1614–21
50. Reineck, H. J., Stein, J. H., Seldin, D. W. 1985. Integrated responses of the kidney to alterations in extracellular fluid volume. See Ref. 31, pp. 1137–61
51. Robertson, G. L. 1977. The regulation of vasopressin function in health and disease. *Rec. Prog. Horm. Res.* 33:333–85
52. Robertson, G. L. 1978. Cancer and inappropriate antidiuresis. In *Biological Markers of Neoplasia: Basic and Applied Aspects,* ed. R. W. Rudden, pp. 277–93. New York: Elsevier North-Holland
53. Robertson, G. L. 1979. Physiopathology of ADH secretion. In *Clinical Neuroendocrinology: A Pathophysiological Approach,* ed. G. Tolis, J. B. Martin, F. Naltolin, pp. 247–60. New York: Raven
54. Robertson, G. L. 1980. Psychogenic polydipsia and inappropriate antidiuresis. *Arch. Intern. Med.* 140:1574–75
55. Robertson, G. L. 1984. Abnormalities of thirst regulation. *Kidney Int.* 25:460–69
56. Robertson, G. L. 1987. Posterior pituitary. In *Endocrinology and Metabolism,* ed. P. Felig, J. Baxter, A. E. Broadus, L. A. Frohman, pp. 339–86. New York: McGraw-Hill. 2nd ed.
57. Robertson, G. L., Athar, S. 1976. The interaction of blood osmolality and blood volume in regulating plasma vasopressin in man. *J. Clin. Endocrinol. Metab.* 42:613–20
58. Robertson, G. L., Berl, T. 1985. Water metabolism. In *The Kidney,* ed. B. M. Brenner, F. C. Rector, pp. 385–432. Philadelphia: Saunders. 3rd ed.
59. Robertson, G. L., Oiso, Y., Vokes, T. P., Gaskill, M. B. 1985. Diprenorphine inhibits selectively the vasopressin response to hypovolemic stimuli. *Trans. Assoc. Am. Physicians* 48:322–33
60. Robertson, G. L., Shelton, R. L., Athar, S. 1976. The osmoregulation of vasopressin. *Kidney Int.* 10:25–37
61. Robinson, A. G., Verbalis, J. G. 1985. Biosynthesis, transport and release of vasopressin. *Front. Horm. Res.* 13:22–36
62. Rogers, P. W., Kurtzman, N. A. 1973. Renal failure, uncontrollable thirst, and hyperreninemia. *J. Am. Med. Assoc.* 225(10):1236–38
63. Rowe, J. W., Shelton, R. L., Helderman, J. H., Vestal, R. E., Robertson, G. L. 1979. Influence of the emetic reflex on vasopressin in man. *Kidney Int.* 16:729–35
64. Russell, J. T., Brownstein, M. J., Gainer, H. 1980. Biosynthesis of vasopressin, oxytocin and neurophysins: Isolation and characterization of two common precursors (propressophysin and prooxyphysin). *Endocrinology* 107:1880–91
65. Saudek, C. D., Boulter, P. R., Arky, R. A. 1973. The natriuretic effect of glucagon and its role in starvation. *J. Clin. Endocrinol. Metab.* 36:761–65
66. Sawchenko, P. E., Swanson, L. W. 1981. Central noradrenergic pathways for the integration of hypothalamic neuroendocrine and autonomic responses. *Science* 214:685–87
67. Schaff-Blass, E., Robertson, G. L., Rosenfield, F. L. 1983. Chronic hypernatremia from a congenital defect in osmoregulation of thirst and vasopressin. *J. Pediatr.* 102:703–8
68. Schrier, R. W., Linas, S. L. 1980. Mechanisms of the defect in water excretion in adrenal insufficiency. *Mineral Electrolyte Metab.* 4:1–7
69. Sigler, M. H. 1975. The mechanism of the natriuresis of fasting. *J. Clin. Invest.* 55:377–87
70. Silverman, A. J., Zimmerman, E. A. 1983. Magnocellular neurosecretory system. *Ann. Rev. Neurosci.* 6:357–80
71. Singer, I., Forrest, J. N. Jr. 1976. Drug-induced states of nephrogenic diabetes insipidus. *Kidney Int.* 10:82–95
72. Skorecki, K. L., Brenner, B. M. 1982. Body fluid homeostasis in congestive heart failure and cirrhosis with ascites. *Am. J. Med.* 72:323–38
73. Spruce, B. A., Baylis, P. H., Burd, J., Watson, M. J. 1985. Variation in osmoregulation of arginine vasopressin during the human menstrual cycle. *Clin. Endocrinol.* 22:37–42
74. Stuart, C. A., Neelon, F. A., Lebovitz,

H. E. 1980. Disordered control of thirst in hypothalamic-pituitary sarcoidosis. *N. Engl. J. Med.* 303:1078–82
75. Thames, M. D., Schmid, P. G. 1979. Cardiopulmonary receptors with vagal afferents tonically inhibit ADH release in the dog. *Am. J. Physiol.* 237:H299–H304
76. Szatalowicz, V. L., Arnold, P. E., Chaimovitz, C., Bichet, D., Berl, T., Schreir, R. W. 1981. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *N. Engl. J. Med.* 305:263–66
77. Thrasher, T. N., Brown, C. J., Keil, L. C., Ramsay, D. J. 1980. Thirst and vasopressin release in the dog: An osmoreceptor or sodium receptor mechanism? *Am. J. Physiol.* 238:R333–39
78. Thrasher, T. N., Keil, L. C., Ramsay, D. J. 1982. Hemodynamic, hormonal, and drinking responses to reduced venous return in the dog. *Am. J. Physiol.* 243(12):R354–62
79. Thrasher, T. N., Nistal-Herrera, J. H., Keil, L. C., Ramsay, D. J. 1981. Satiety and inhibition of vasopressin secretion after drinking in dehydrated dogs. *Am. J. Physiol.* 240(3):E394–E401
80. Uretsky, B. F., Verbalis, J. G., Generalovich, T., Valdes, A., Reddy, P. S. 1985. Plasma vasopressin response to osmotic and hemodynamic stimuli in heart failure. *Am. J. Physiol.* 248:H396–H402
81. Usberti, M., Federico, S., Meccariello, S., Cianciaruso, B., Balleta, M., et al. 1984. Role of plasma vasopressin in the impairment of water excretion in nephrotic syndrome. *Kidney Int.* 25: 422–29
82. Verbalis, J. G., Robinson, A. G. 1983. Characterization of neurophysin-vasopressin prohormones in human posterior pituitary tissue. *J. Clin. Endocrinol. Metab.* 57:115–23
83. Veverbrants, E., Arky, R. A. 1969. Effects of fasting and refeeding. I. Studies on sodium, potassium and water excretion on a constant electrolyte and fluid intake. *J. Clin. Endocrinol.* 29:55–62
84. Verney, E. B. 1947. Antidiuretic hormone and the factors which determine its release. *Proc. R. Soc. London Ser. B* 135:25–106
85. Vokes, T. P., Aycinena, P. R., Robertson, G. L. 1987. Effect of insulin on the osmoregulation of vasopressin. *Am. J. Physiol.* E538-48
86. Vokes, T., Gaskill, M., Robertson, G. L. 1984. Changes in the osmoregulation of thirst and vasopressin during the normal menstrual cycle. *Excerpta Med.* 652:2666 (Abstr.)
87. Vokes, T., Robertson, G. L. 1985. Physiology and secretion of vasopressin. *Front. Horm. Res.* 13:127–55
88. Vokes, T., Robertson, G. L. 1985. Clinical effects of altered vasopressin secretion. In *Neuroendocrine Perspectives,* ed. E. E. Muller, R. M. MacLeod, L. A. Frohman, 4:1–41. Amsterdam: Elsevier Science
89. Walsh, C. H., Baylis, P. H., Malins, J. M. 1979. Plasma arginine vasopressin in diabetic ketoacidosis. *Diabetologia* 16: 93–96
90. Wang, B. C., Sundet, W. D., Hakumaki, M. O. K., Geer, P. G., Goetz, K. L. 1984. Cardiac receptor influences on the plasma osmolality-plasma vasopressin relationship. *Am. J. Physiol.* 246(15): H360–68
91. Wang, B. C., Sundet, W. D., Hakumaki, M. O. K., Goetz, K. L. 1983. Vasopressin and renin responses to hemorrhage in conscious, cardiac-denervated dogs. *Am. J. Physiol.* 245(14):H399–H405
92. Weiss, N. M., Robertson, G., Byun, K. 1984. The effect of hypovolemia on the osmoregulation of thirst and AVP. *Clin. Res.* 32(4):786A (Abstr.)
93. Williams, R. H., Henry, C. 1947. Nephrogenic diabetes insipidus: Transmitted by females and appearing during infancy in males. *Ann. Intern. Med.* 27:84–95
94. Zerbe, R. L., Robertson, G. L. 1981. A comparison of plasma vasopressin measurements with a standard indirect test in the differential diagnosis of polyuria. *N. Engl. J. Med.* 305:1539–46
95. Zerbe, R. L., Robertson, G. L. 1983. Osmoregulation of thirst and vasopressin secretion in human subjects: Effect of various solutes. *Am. J. Physiol.* 224: E607–14
96. Zerbe, R. L., Stropes, L., Robertson, G. L. 1980. Vasopressin function in the syndrome of inappropriate antidiuresis. *Ann. Rev. Med.* 31:315–27
97. Zerbe, R. L., Viñicor, F., Robertson, G. L. 1979. Plasma vasopressin in uncontrolled diabetes mellitus. *Diabetes* 28(5):503–8