SECTION 1 | THE PITUITARY GLAND

CHAPTER 1 | Water Metabolism and Diabetes Insipidus

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Water consumption and urine production are controlled by complex interactions between plasma osmolality, fluid volume in the vascular compartment, the thirst center, the kidney, the pituitary gland, and the hypothalamus. Dysfunction in any of these areas results in the clinical signs of polyuria and polydipsia. Arginine vasopressin (AVP) plays a key role in the control of renal water resorption, urine production and concentration, and water balance. In the presence of vasopressin and dehydration, the average dog and cat can produce urine concentrated to or above 2300 mOsm/kg of H_2O. In the absence of vasopressin or vasopressin action on the kidneys, the urine may be as dilute as 20 mOsm/kg of H_2O.

Diabetes insipidus results from deficiencies in secretion of vasopressin or in its ability to interact normally with receptors located in the distal and collecting tubular cells of the kidney. The result of either disorder is impaired ability to conserve water and concentrate urine, with production of large volumes of hypotonic dilute urine and compensatory often severe polydipsia to minimize dehydration. Because of the dramatic polyuria and polydipsia associated with diabetes mellitus and diabetes insipidus, the term *diabetes* (secretion of a large volume of urine) was historically used for both conditions. However, the urine is tasteless (insipid) with diabetes insipidus because, unlike in diabetes mellitus (in which the urine is sweet from sugar), polyuria in
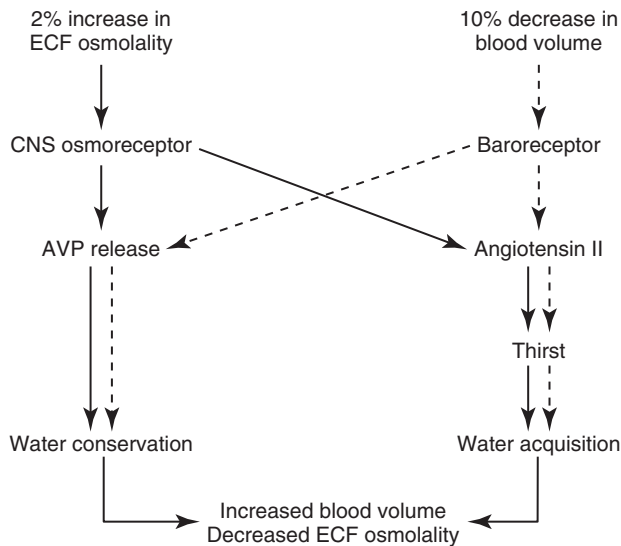
FIGURE 1-1 Schematic illustration of the primary mechanisms involved in maintenance of water balance. *Solid lines* indicate osmotically stimulated pathways, and *dashed lines* indicate volume stimulated pathways. (Adapted from Reeves WB, Andreoli TE: The posterior pituitary and water metabolism. In Wilson JD, Foster DW, editors: *Williams textbook of endocrinology,* ed 8, Philadelphia, 1992, WB Saunders, p. 311.) *AVP,* Arginine vasopressin; *CNS,* central nervous system; *ECF,* extracellular fluid.

diabetes insipidus is not the result of a glucose-induced osmotic diuresis.

PHYSIOLOGY OF WATER METABOLISM

Plasma osmolality and its principal determinant, the plasma sodium concentration, are normally maintained within remarkably narrow ranges. This stability is achieved largely by adjusting total body water to keep it in balance with the serum sodium concentration. Water balance is controlled by an integrated system that involves regulation of water intake by the thirst center and control of urine volume by plasma vasopressin (Fig. 1-1). The physiologic regulation of vasopressin synthesis and secretion involves two systems: extracellular fluid (ECF) osmolality and blood pressure and volume. Vasopressin is the main hormone involved in the regulation of water homeostasis and osmolality and the renin-angiotensin-aldosterone system (RASS) is mainly responsible for regulation of blood pressure and volume (Robinson and Verbalis, 2011). Regarding osmoregulation, vasopressin secretion is relatively uncomplicated, with small increases in osmolality producing a parallel increase in vasopressin secretion and small decreases in osmolality causing a parallel decrease in vasopressin secretion.

The Neurohypophysis

The neurohypophysis consists of a set of hypothalamic nuclei (supraoptic and paraventricular) containing magnocellular neurons responsible for the synthesis of oxytocin and vasopressin; the axonal processes of these cells, which form the supraopticohypophysial tract; and the termini of these cells within the posterior lobe of the pituitary (Fig. 1-2; Reeves et al, 1998). The magnocellular neurons in the paraventricular and supraoptic nuclei secrete vasopressin or oxytocin in response to appropriate stimuli. The magnocellular neurons producing vasopressin receive neurogenic input from various sensor elements, including high-pressure arterial baroreceptors
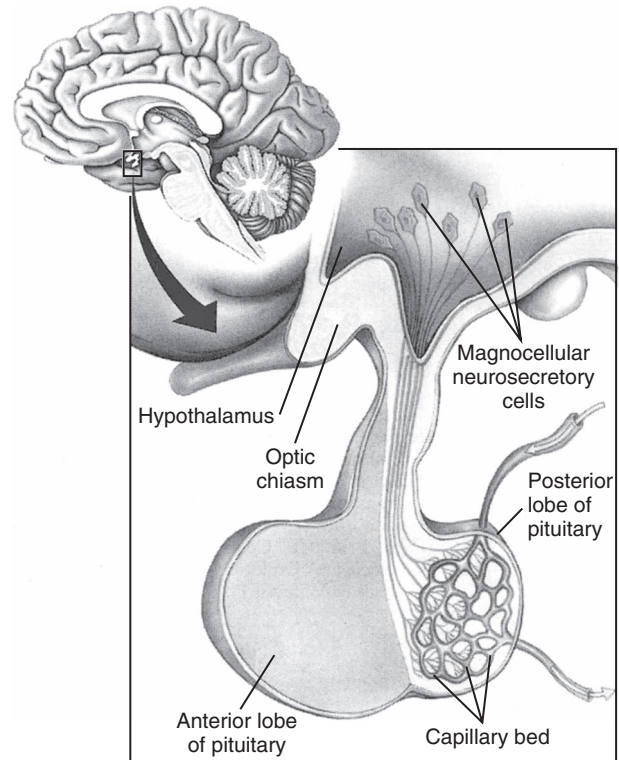

FIGURE 1-2 Midsagittal view of the hypothalamus and pituitary gland illustrating the cell bodies of the magnocellular neurons in the hypothalamus and extension of their axons into the pituitary gland where vasopressin and oxytocin are secreted directly into capillaries in the posterior lobe of the pituitary gland. (From Bear MF, et al.: *Neuroscience: exploring the brain,* ed 3, Baltimore, 2007, Lippincott Williams & Wilkins, p. 486.)

located in the carotid sinus and aortic arch and low-pressure volume receptors located in the atria and pulmonary venous system (Thrasher, 1994). Baroreceptors and volume receptors normally inhibit the magnocellular neurons, and decreases in this tonic inhibition result in the release of vasopressin. Arterial and venous constriction induced by vasopressin action on V_{1a} receptors on blood vessels contracts the vessels around the existing plasma volume to effectively "increase" plasma volume and reestablish the inhibition of secretion of vasopressin (Robinson and Verbalis, 2011). Vasopressin's action at the kidney to retain water does help replace volume, but the major hormonal regulation to control blood volume is the RAAS, which stimulates sodium reabsorption in the kidney.

Vasopressin: Biosynthesis, Transport, and Metabolism

Vasopressin and oxytocin are nonapeptides composed of a six-membered disulfide ring and a three-membered tail on which the terminal carboxyl group is amidated (Fig. 1-3). AVP is the antidiuretic hormone in all mammals except swine and other members of the suborder Suina, in which lysine vasopressin is synthesized (Reeves et al, 1998). Vasopressin differs from oxytocin in most mammals only in the substitution of phenylalanine for isoleucine in the ring and arginine for leucine in the tail. The ratio of antidiuretic to pressor effects of vasopressin is increased markedly by substituting d-arginine for l-arginine at position 8. This modification, as well as removal of the terminal amino group from cysteine, yields desmopressin acetate (DDAVP), a synthetic commercially available product (see Fig. 1-3). DDAVP is a clinically useful analogue with prolonged and enhanced antidiuretic activity that does
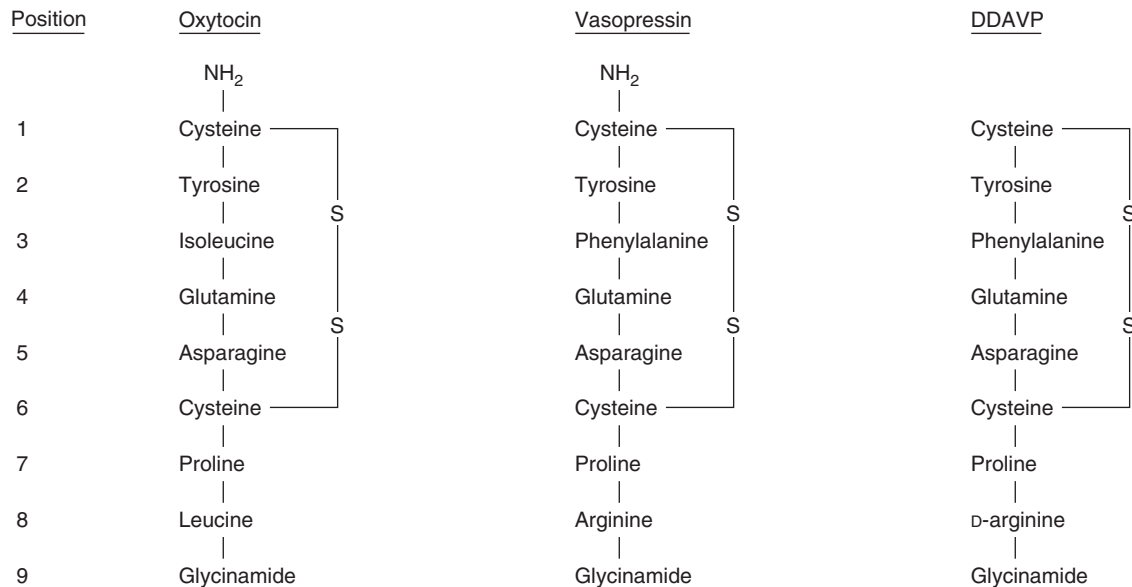
Position	Oxytocin	Vasopressin	DDAVP
	NH$_2$	NH$_2$	
1	Cysteine	Cysteine	Cysteine
2	Tyrosine	Tyrosine	Tyrosine
3	Isoleucine	Phenylalanine	Phenylalanine
4	Glutamine	Glutamine	Glutamine
5	Asparagine	Asparagine	Asparagine
6	Cysteine	Cysteine	Cysteine
7	Proline	Proline	Proline
8	Leucine	Arginine	D-arginine
9	Glycinamide	Glycinamide	Glycinamide

FIGURE 1-3 The chemical structures of oxytocin, vasopressin, and 1 desmopressin acetate (DDAVP).

not require injection to be effective and is commonly used to treat central diabetes insipidus (CDI) in dogs and cats.

The production of vasopressin and oxytocin is associated with synthesis of specific binding proteins called *neurophysins.* One molecule of neurophysin I binds one molecule of oxytocin and one molecule of neurophysin II binds one molecule of vasopressin (Reeves et al, 1998). The neurophysin peptide combination, often referred to as *neurosecretory material,* is transported along the axons of the hypothalamo-neurohypophyseal nerve tract and stored in granules in the nerve terminals located in the posterior pituitary gland (see Fig. 1-2). Release of vasopressin into the bloodstream occurs following electrical activation of the magnocellular neurons containing AVP. Secretion proceeds by a process of exocytosis, with release of vasopressin and neurophysin II into the bloodstream. In plasma, the neurophysin-vasopressin combination dissociates to release free vasopressin. Nearly all of the hormone in plasma exists in an unbound form, which because of its relatively low molecular weight, readily permeates peripheral and glomerular capillaries. Metabolic degradation of AVP appears to be mediated through binding of AVP to specific receptors, with subsequent proteolytic cleavage of the peptide (Reeves et al, 1998). Renal excretion is the second method for elimination of circulating AVP and accounts for about one-fourth of total metabolic clearance.

Actions of Vasopressin

AVP binds to cellular receptors at the end organs of response. The antidiuretic action of AVP is mediated through V$_2$ cyclic adenosine monophosphate (AMP)-dependent receptors on renal collecting duct epithelia, whereas its vasoconstrictive action is mediated through V$_{1a}$ phosphatidylinositol dependent receptors on blood vessels. A third receptor (V$_3$ or V$_{1b}$) is responsible for the nontraditional biologic action of vasopressin to stimulate adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary. V$_2$ receptors also regulate the nontraditional action of vasopressin to stimulate production of factor VIII and von Willebrand factor (Robinson and Verbalis, 2011). The vasopressin analogue, DDAVP, which is commonly used for the treatment of CDI, has a strong affinity for V$_2$ receptors with minimal pressor (V$_1$) activity.

The primary receptors for sensing changes in osmolality are located in the brain and, specifically cells in the organum vasculosum of the lamina terminalis and in areas of the adjacent anterior hypothalamus near the anterior wall of the third cerebral ventricle (Robinson and Verbalis, 2011). Because cells in these areas are perfused by fenestrated capillaries, the blood brain barrier is deficient, the cells are influenced by the composition of plasma rather than cerebrospinal fluid (CSF) and are able to invoke a rapid change in vasopressin secretion in response to changes in plasma osmolality. As little as a 1% increase or decrease in plasma osmolality causes a rapid increase or decrease of vasopressin from the store of hormone in the posterior pituitary. Rapid metabolism of vasopressin (half-life of approximately 15 minutes) also allows rapid changes in the concentration of vasopressin in plasma.

In the kidney, water is conserved by the combined functions of the loop of Henle and the collecting duct. The loop of Henle generates a high osmolality in the renal medulla by means of the countercurrent multiplier system. Vasopressin acts to increase the water permeability of the collecting duct, thereby allowing osmotic equilibration between the urine and the hypertonic medullary interstitium. The effects of AVP are mediated primarily by the intracellular second messenger cyclic adenosine monophosphate (cAMP) (Fig. 1-4). AVP binds to the V$_2$ receptors of hormone-responsive epithelial cells and activates membrane-associated adenylate cyclase to catalyze cAMP generation from adenosine triphosphate (ATP). cAMP-dependent activation of protein kinase A leads to an increase in water permeability of the luminal membrane of the cell as a result of insertion of aquaporin-2 water channels into the apical membrane of the epithelial cell. Transmembrane water movement occurs through these water channels, rather than by diffusion across the lipid bilayer or through junctional complexes (Fig. 1-5; Robben et al, 2006). In essence, AVP, working via cAMP and protein kinase A, alters water transport in hormone-responsive epithelia by causing the microtubule-dependent insertion of specialized membrane units (aquaporin-2 water channels) into the apical plasma membranes of these cells. The increase in water permeability in these segments augments osmotic water flow from the tubular lumen into a hypertonic medullary interstitium. Blood vessels in the interstitium (i.e., vasa recta) distribute absorbed water into the systemic circulation, maintaining the hypertonicity of the medullary interstitium. The net effect of this process is to extract water from the
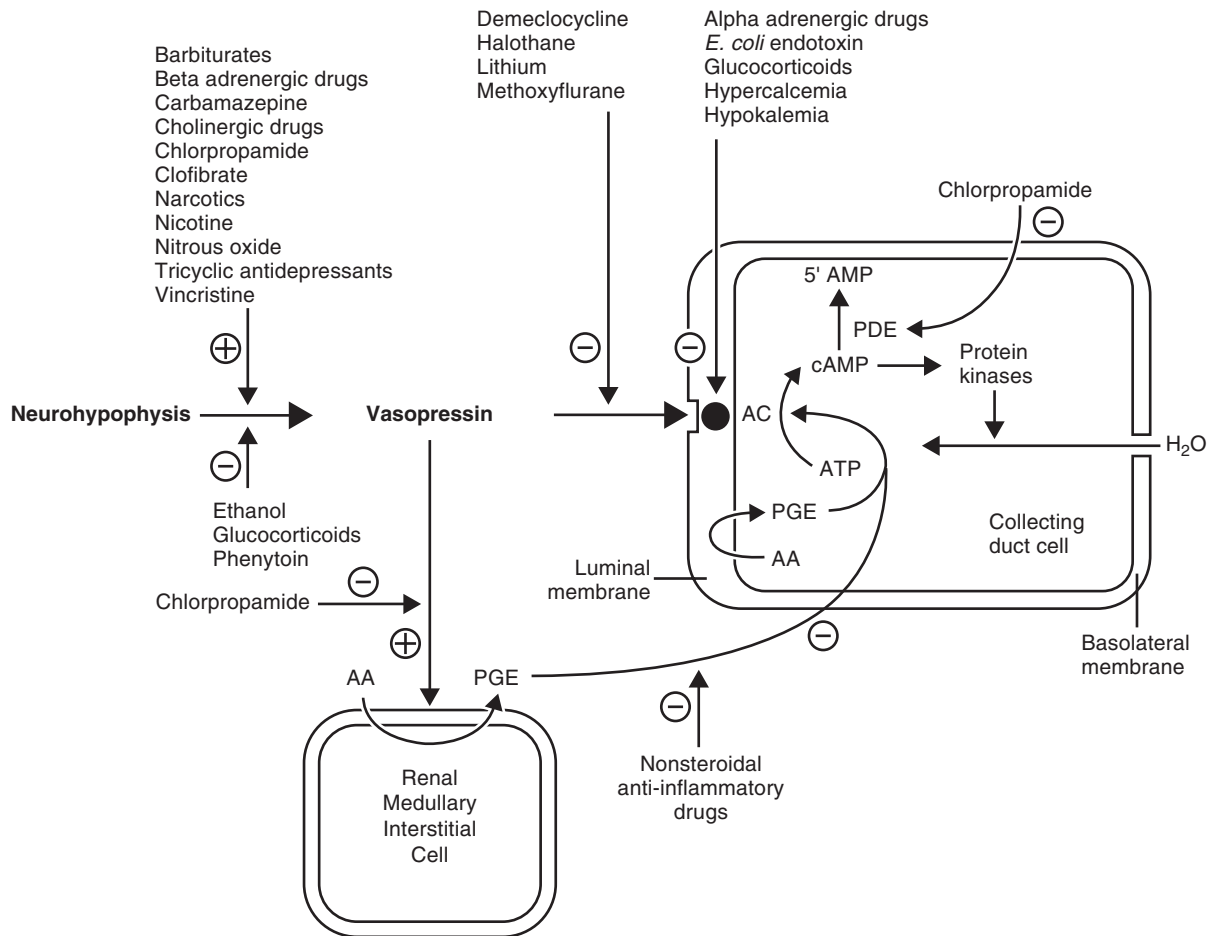
Barbiturates
Beta adrenergic drugs
Carbamazepine
Cholinergic drugs
Chlorpropamide
Clofibrate
Narcotics
Nicotine
Nitrous oxide
Tricyclic antidepressants
Vincristine

Demeclocycline
Halothane
Lithium
Methoxyflurane

Alpha adrenergic drugs
E. coli endotoxin
Glucocorticoids
Hypercalcemia
Hypokalemia

Chlorpropamide

5' AMP

PDE

cAMP → Protein kinases

AC

ATP

H_2O

PGE

AA

Collecting duct cell

Neurohypophysis → **Vasopressin**

Luminal membrane

Basolateral membrane

Ethanol
Glucocorticoids
Phenytoin

Chlorpropamide

AA   PGE

Renal Medullary Interstitial Cell

Nonsteroidal anti-inflammatory drugs

FIGURE 1-4 Effects of selected drugs and electrolytes on vasopressin release and action. (From DeBartola SP: Disorders of sodium and water: hypernatremia and hyponatremia. In DiBartola SP, editor: *Fluid therapy in small animal practice,* ed 2, Philadelphia, 2000, WB Saunders, p. 52.) *5'AMP,* 5'-adenosine monophosphate, *AA,* arachidonic acid; *AC,* adenyl cyclase; *ATP,* adenosine triphosphate; *cAMP,* cyclic adenosine monophosphate; *PDE,* phosphodiesterase; *PGE,* prostaglandin E.

urine, resulting in increased urine concentration and decreased urine volume. Dissociation of AVP from the V_2 receptor allows intracellular cAMP levels to decrease and the water channels are then reinternalized, terminating the increased water permeability.

The primary effect of AVP is to conserve body fluid by reducing the volume of urine production (Table 1-1). This antidiuretic action is achieved by promoting the reabsorption of solute free water in the distal and/or collecting tubules of the kidney. In the absence of AVP, the membranes lining this portion of the nephron are uniquely resistant to the diffusion of both water and solutes. Hence the hypotonic filtrate formed in the more proximal portion of the nephron passes unmodified through the distal tubule and collecting duct. In this condition, referred to as *water diuresis,* urine osmolality is low and urine volume is great (see Fig. 1-5).

The amount of water reabsorbed in the distal nephron depends on the plasma AVP concentration and the existence of a significant osmotic gradient in the renal interstitium. Vasopressin does not cause an active (i.e., energy-requiring) reabsorption of solute free water. It merely "opens the water channels" in the luminal membrane to allow water to flow in the direction of the higher osmolality (along the osmotic gradient). In the normal animal, the osmolality of the filtrate entering the distal tubule is low, whereas that of the renal interstitium is high, promoting reabsorption of water when the pores are open. Increasing the renal medullary interstitial osmolality increases the ability to reabsorb water and

concentrate urine; thus desert rodents with extremely concentrated medullary interstitium can produce urine more concentrated than that of dogs and are remarkably capable of conserving fluid. Conversely, loss of the renal medullary hypertonicity may inhibit vasopressin's antidiuretic activity (see Fig. 1-5). Decreased medullary hypertonicity (or lack thereof) can result from various causes, such as chronic water diuresis or reduced medullary blood flow. However, because a majority of fluid flowing from the loop of Henle can still be reabsorbed isotonically in the distal convoluted tubule and proximal collecting duct, loss of the hypertonic medullary concentration gradient alone rarely results in marked polyuria (Robertson, 1981).

It should be noted that 85% to 90% of the fluid filtered by the glomerulus is reabsorbed isosmotically with sodium and glucose in the proximal portion of the nephron. Sodium is then selectively reabsorbed from the remaining fluid, making the fluid hypotonic as it reaches the distal nephron. An additional 90% of this remaining fluid can be reabsorbed under the influence of AVP (Robertson, 1981). However, if the oral intake of salt is high or if a poorly reabsorbed solute such as mannitol, urea, or glucose is present in the glomerular filtrate, fluid resorption from the proximal tubule is impaired. The resultant increase in fluid volume presented to the distal nephron may overwhelm its limited capacity to reabsorb water. As a consequence, urine osmolality decreases and volume increases, even in the presence of large amounts of vasopressin.
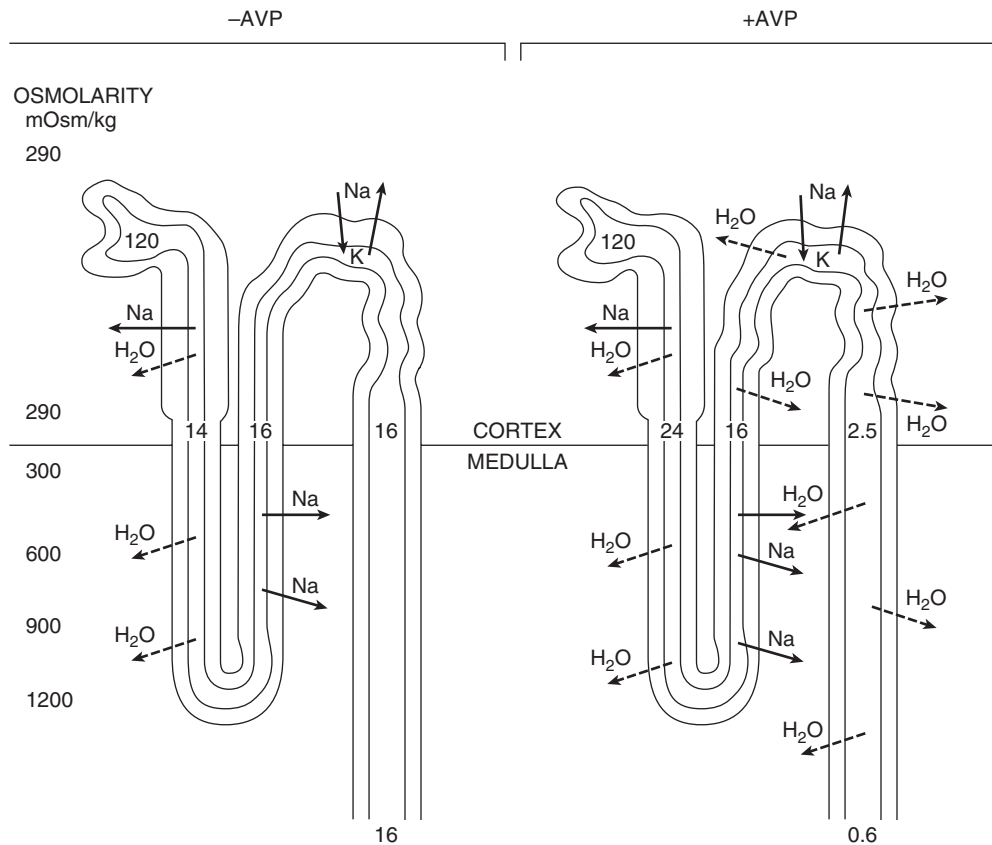
FIGURE 1-5 Schematic representation of the effect of vasopressin on the formation of urine by the human nephron. The osmotic pressure of tissue and tubular fluid is indicated by the density of the shading. The numbers within the lumen of the nephron indicate typical rates of flow in milliliters per minute. *Arrows* indicate reabsorption of sodium (Na) or water (H_2O) by active *(solid arrows)* or passive *(broken arrows)* processes. Note that vasopressin acts only on the distal nephron, where it increases the hydro-osmotic permeability of tubular membranes. The fluid that reaches this part of the nephron normally amounts to between 10% and 15% of the total filtrate and is hypotonic owing to selective reabsorption of sodium in the ascending limb of the loop of Henle. In the absence of vasopressin, the membranes of the distal nephron remain relatively impermeable to water, as well as to solute, and the fluid issuing from the loop of Henle is excreted essentially unmodified as urine. With maximum vasopressin action, all but 5% to 10% of the water in this fluid is reabsorbed passively down the osmotic gradient that normally exists with the surrounding tissue. Remember that the concentration of the canine renal medullary interstitial fluid can be greater than 2500 mOsm/kg. (Reprinted with permission from Robertson GL: Posterior pituitary. In Felig P, et al. (eds): *Endocrinology and metabolism*, ed 2, New York, 1987, McGraw Hill Book Co, p. 351.)

TABLE 1-1	**ACTIONS OF VASOPRESSIN**	
TARGET ORGAN	**TYPE OF RECEPTOR**	**ACTION**
Kidney		
Cortical and medullary collecting ducts	V_2	Enhances water permeability
Thick ascending limb of the loop of Henle	V_2	Enhances Na^{2+}, Cl^-, K^+ reabsorption
Juxtaglomerular cells	V_1	Suppresses renin release
Cardiovascular system		
Arterioles	V_1	Vasoconstriction
Coagulation system	V_2	Stimulate von Willebrand factor Stimulate antihemophiliac factors
Pituitary gland	V_3	Stimulate ACTH secretion

ACTH, Adrenocorticotropic hormone.

This type of polyuria is referred to as solute diuresis to distinguish it from that due to a deficiency of vasopressin action.

Thirst

Consumption of water to preserve body fluid tonicity is governed by the sense of thirst, which in turn is regulated by many of the same factors that determine AVP release (Fig. 1-6). Thirst can be stimulated by increases in ECF osmolality and by decreases in intravascular volume. Osmoreceptors in the anterior hypothalamus and low- and high-pressure baroreceptors in the thorax mediate the thirst stimulus. Circulating angiotensin II may also stimulate thirst when hypovolemia and hypotension are severe (Stocker et al, 2000). Studies in humans using quantitative estimates of subjective symptoms of thirst have confirmed that increases in plasma osmolality of 2% to 3% are necessary to produce an unequivocal sensation of thirst (Baylis and Thompson, 1988).

Satiation of Thirst

Dehydrated animals have a remarkable capacity to consume the appropriate volume of water to repair a deficit. It has been
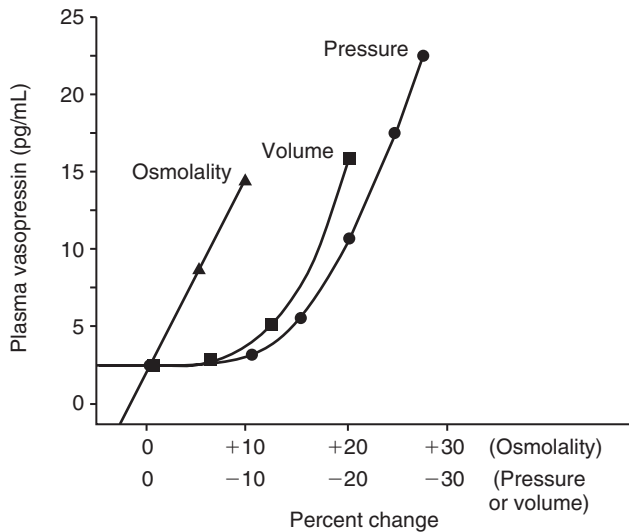
FIGURE 1-6 The relationship between plasma osmolality and plasma vasopressin level. (Adapted from Robertson GL, Berl T: Water metabolism. In Brenner BM, Rector FC Jr, editors: *The kidney,* ed 3, Philadelphia,1986, WB Saunders, p. 385.)

demonstrated that dogs deprived of water for various periods of time drink just the volume of water needed to meet the deficit within 5 minutes. All animals have this capacity, although some species take longer to ingest the required amount of fluid. Satiation of thirst in dogs and cats requires restoration of normal plasma osmolality and blood volume, with correction of plasma osmolality playing the major role. In dogs with hypertonic volume depletion, restoration of osmolality in the carotid circulation without correcting osmolality outside the central nervous system (CNS) caused a 70% decrease in drinking (Reeves et al, 1998). Restoration of blood volume in these dogs without ameliorating plasma hypertonicity reduced drinking by about 30%. Additional mechanisms may also play a minor role, including gastric distention and perhaps the participation of receptors in the liver. Similar inhibitory influences affect vasopressin secretion. Following voluntary rehydration in dehydrated animals, plasma vasopressin secretion returns to normal before redilution of the body fluids has been completed.

DIFFERENTIAL DIAGNOSES FOR POLYDIPSIA AND POLYURIA

Increased thirst (polydipsia) and urine production (polyuria) are common owner concerns in small animal veterinary practice. In dogs, normal water intake is usually less than 80 mL/kg of body weight/24 h. Water intake between 80 and 100 mL/kg/24 h is suggestive of polydipsia but may be normal in some dogs. Water intake greater than 100 mL/kg/24 h confirms polydipsia. Similar values are used for cats, although most cats drink considerably less than these amounts. Normal urine output varies between 20 and 45 mL/kg/24 h (1 to 2 mL/kg/h; Barsanti et al, 2000). Polyuria in the dog and cat has been defined as urine production greater than 50 mL/kg/24 h, respectively, although it is possible for urine production to be abnormal within the limits of these normal values in individual dogs and cats. Polyuria and polydipsia usually exist concurrently, and determining the primary component of the syndrome is one of the initial diagnostic considerations when approaching the problem of polydipsia and polyuria (see Diagnostic Approach to Polyuria and Polydipsia later in this chapter).

A variety of metabolic disturbances can cause polydipsia and polyuria (Table 1-2). Primary polyuric disorders can be classified on the basis of the underlying pathophysiology into primary pituitary and nephrogenic diabetes insipidus (NDI), secondary NDI, osmotic diuresis-induced polyuria, and interference with the hypothalamic-pituitary secretion of AVP. The most common form of diabetes insipidus is acquired secondary NDI. This form includes a variety of renal and metabolic disorders in which the renal tubules lose the ability to respond adequately to AVP. Most of these acquired forms are potentially reversible after elimination of the underlying illness.

Secondary NDI results from interference with the normal interaction of AVP and renal tubular AVP receptors, problems with the generation of intracellular cAMP, problems with renal tubular cell function, or loss of the renal medullary interstitial concentration gradient. Primary polydipsic disorders occur in dogs and usually have a psychogenic or behavioral basis for the compulsive water consumption.

Osmotic Diuresis

Diabetes Mellitus

Diabetes mellitus is one of the most common endocrinopathies in the dog and cat. As glucose utilization diminishes as a result of relative or absolute insulin deficiencies, glucose accumulates in the blood. When the rising blood glucose concentration exceeds the renal tubular capacity for glucose reabsorption, glucose appears in the urine and acts as an osmotic diuretic, causing increased water loss into the urine. The water loss results in hypovolemia, which in turn stimulates increased water intake. Urinalysis and fasting blood glucose measurement are usually sufficient screening tests for diagnosing diabetes mellitus.

Primary Renal Glycosuria

This uncommon disorder is seen primarily in the Basenji and Norwegian Elkhound. Primary renal glycosuria is a congenital renal tubular disorder resulting in an inability to reabsorb glucose from the ultrafiltrate in the nephron. In some dogs and cats, renal glycosuria may also be a component of a Fanconi-like syndrome, in which phosphate, potassium, uric acid, amino acids, sodium, and/or bicarbonate may also be inadequately reabsorbed from the ultrafiltrate. As in diabetes mellitus, glucose appears in the urine and acts as an osmotic diuretic, causing polyuria and, in turn, polydipsia. Primary renal glycosuria should be suspected in a dog with polyuria and polydipsia, persistent glycosuria, and normal blood glucose and serum fructosamine concentrations. Urinalysis and fasting blood glucose measurement are sufficient initial screening tests for this disorder.

Chronic Renal Failure

Chronic renal failure is a syndrome in which the number of functioning nephrons progressively decreases as a result of structural damage to the kidney, as occurs with chronic interstitial nephritis, medullary interstitial amyloidosis, and chronic pyelonephritis. A compensatory increase is seen in glomerular filtration rate (GFR) per surviving nephron, but the amount of fluid presented to the distal renal tubules is increased. Increased tubular flow rate causes less urea, sodium, and other substances to be reabsorbed. The result is an osmotic diuresis that is further complicated by a reduced renal medullary concentration gradient. These factors contribute to polyuria. The water loss results in hypovolemia, which causes compensatory polydipsia. Findings on routine blood and urine tests include increased blood urea nitrogen (BUN), creatinine, and inorganic phosphorus concentrations, nonregenerative anemia and isosthenuric urine (urine specific gravity of 1.008 to 1.015).

TABLE 1-2 **DIFFERENTIAL DIAGNOSIS FOR POLYDIPSIA AND POLYURIA AND USEFUL DIAGNOSTIC TESTS**

DISORDER	DIAGNOSTIC AIDS
Diabetes mellitus	Fasting blood glucose, urinalysis
Renal glycosuria	Fasting blood glucose, urinalysis
Chronic renal failure	History, physical exam, BUN, creatinine, Ca:P, urinalysis
Polyuric acute renal failure	History, physical exam, BUN, creatinine, Ca:P, urinalysis
Postobstructive diuresis	History, monitoring urine output
Pyometra	History of recent estrus, CBC, abdominal radiography, abdominal ultrasonography
Escherichia coli and septicemia	Blood cultures
Hypercalcemia	Serum calcium
Hepatic insufficiency	Biochemistry panel, bile acids, ammonia tolerance test, abdominal radiography and ultrasonography
Hyperadrenocorticism	Physical exam, chemistry panel, abdominal ultrasonography, urine cortisol/creatinine ratio, low-dose dexamethasone suppression test
Primary hyperaldosteronism	Serum sodium and potassium, blood pressure, abdominal ultrasonography, baseline plasma aldosterone
Bacterial pyelonephritis	Urine culture, abdominal ultrasonography, excretory urography
Hypokalemia	Serum potassium
Hyponatremia	Serum sodium
Hypoadrenocorticism	Na:K, baseline serum cortisol, ACTH stimulation test
Hyperthyroidism	Serum T_4 and TSH
Diabetes insipidus	Modified water deprivation test, response to DDAVP
Psychogenic polydipsia	Modified water deprivation test, response to gradual water restriction
Renal medullary solute washout	Response to gradual water restriction
Polycythemia	CBC
Acromegaly	Physical exam, serum GH and IGF-I, CT scan
Paraneoplastic Disorders	
Intestinal leiomyosarcoma	Abdominal ultrasonography, biopsy
Iatrogenic; medications	History
Very low protein diet	History

ACTH, Adrenocorticotropic hormone; *BUN,* blood urea nitrogen; *Ca:P,* calcium:phosphorus; *CBC,* complete blood count; *CT,* computed tomography; *DDAVP,* desmopressin acetate; *GH,* growth hormone; *IGF-I,* insulin-like growth factor-I; T_4, thyroxine; *TSH,* thyroid stimulating hormone.

Postobstructive Diuresis

Postobstructive diuresis may occur in any animal but is most common after urethral obstruction by a urolith or urethral plug is relieved in male cats with feline lower urinary tract disease (e.g., feline interstitial cystitis). Obstructed male cats often develop postrenal azotemia and electrolyte and acid-base disturbances that can be severe. A marked osmotic diuresis usually occurs once the obstruction is relieved. The veterinarian must be aware of this problem and maintain the animal's hydration through frequent adjustments in intravenous (IV) fluid administration aimed at matching urine production. Postobstructive diuresis is self-limiting and the rate of fluid administration should be slowly decreased over several days as the uremia resolves and the osmotic diuresis declines.

Primary Pituitary (Central) Diabetes Insipidus

Partial or complete lack of vasopressin production by the magnocellular neurons located in the supraoptic and paraventricular nuclei in the hypothalamus is called *primary CDI.* This syndrome is discussed in subsequent sections.

Primary Nephrogenic Diabetes Insipidus

A partial or complete lack of response of the renal tubule to the actions of AVP is called *nephrogenic diabetes insipidus (NDI).*

Primary NDI results from a congenital defect involving the cellular mechanisms responsible for "opening the water channels" that allow water to be absorbed from the renal tubular ultrafiltrate. This syndrome is discussed in subsequent sections (see Primary Nephrogenic Diabetes Insipidus).

Acquired (Secondary) Nephrogenic Diabetes Insipidus

Several disorders may interfere with the normal interaction between AVP and its renal tubular AVP receptors, affect the generation of intracellular cAMP, create problems with renal tubular cell function, or result in loss of the hypertonic renal medullary interstitial gradient. Polyuria with a compensatory polydipsia results and can be quite severe. These disorders resemble primary NDI but are referred to as acquired or secondary because AVP, AVP receptor sites, and postreceptor mechanisms responsible for water absorption are present.

Bacterial Endotoxins (Pyometra)

Bacterial endotoxins, especially those associated with *Escherichia coli,* may compete with AVP for its binding sites on the renal tubular membrane, causing a potentially reversible renal tubular insensitivity to AVP, interference with the insertion of aquaporin-2 water channels in renal tubular cells or reversible renal tubular cell lesions (Heiene et al, 2004). The kidneys have an impaired ability to concentrate urine and conserve water, and polyuria with

compensatory polydipsia develops. Pyometra is the most common infectious disorder associated with the development of polyuria and polydipsia, although it has also been reported with prostatic abscessation, pyelonephritis, and septicemia (Barsanti et al, 2000). Affected bitches and queens may produce extremely dilute urine, causing fluid depletion and compensatory polydipsia. Normal urine-concentrating ability usually returns within days of successfully eliminating the source of the infection.

Hypercalcemia

Increases in serum calcium concentration are associated with downregulation of aquaporin-2 water channels and decreased function of AVP by inhibiting binding of AVP to its receptor site, damage to AVP receptors in the renal tubules, inactivation of adenylate cyclase, or decreased transport of sodium and chloride into the renal medullary interstitium (Sands and Bichet, 2006; Robben et al, 2006). Polydipsia and polyuria are common early signs of hypercalcemia, which is easily diagnosed with a serum biochemistry panel. Once hypercalcemia is identified, the clinician must undertake an often extensive diagnostic evaluation to determine its cause (see Chapter 15).

Hepatic Insufficiency and Portosystemic Shunts

Liver insufficiency and portosystemic shunts are recognized causes of polyuria and polydipsia. Many of the metabolic causes of polyuria and polydipsia (e.g., diabetes mellitus, hyperadrenocorticism, hypercalcemia) secondarily affect the liver, making it difficult to determine the role of the liver in causing polyuria and polydipsia. The exact cause of the polyuria is not known but may involve loss of medullary hypertonicity secondary to impaired urea nitrogen production or altered renal blood flow, increased GFR and ultrafiltrate volume, hypokalemia, impaired metabolism of cortisol, and primary polydipsia (Deppe et al, 1999). Urea nitrogen is a major constituent in the establishment and maintenance of the renal medullary concentration gradient. Without urea nitrogen, the kidney loses the ability to concentrate urine, causing polyuria and compensatory polydipsia. Hepatic insufficiency and portosystemic shunts are usually suspected after evaluation of a complete blood count (CBC), serum biochemistry panel, urinalysis, and abdominal ultrasonography; these causes are confirmed with a liver function test (e.g., pre- and postprandial bile acids), specialized diagnostic imaging (e.g., positive contrast portogram, technetium scan) and histologic evaluation of a hepatic biopsy.

Hyperadrenocorticism (Cushing's Syndrome)

Polyuria and polydipsia are common clinical signs of hyperadrenocorticism. Glucocorticoids inhibit AVP release by a direct effect within the hypothalamus and/or neurohypophysis (Papanek and Raff, 1994; Papanek et al, 1997). This inhibition of AVP release is characterized by both an increase in osmotic threshold and a decrease in the sensitivity of the AVP response to increasing osmolality (Biewenga et al, 1991). Glucocorticoids also increase glomerular filtration rate, proximal tubular epithelial sodium transport, and free water clearance and cause resistance to the effect of AVP in the kidney, possibly through interference with the action of AVP at the level of the renal collecting tubules or direct depression of renal tubular permeability to water (Marver, 1984; Quinkler and Stewart, 2003). In a few patients, a deficiency in AVP may result from direct compression of magnocellular neurons by a pituitary macrotumor that has extended beyond the sella. Suspicion of hyperadrenocorticism is usually aroused after careful review of the history, physical examination, and results of CBC, serum biochemistry panel, and urinalysis. Confirmation requires appropriate pituitary adrenocortical function tests (see Chapter 10).

Primary Hyperaldosteronism

Polyuria and polydipsia have been reported in cats and dogs with primary hyperaldosteronism. The mechanism for polyuria and polydipsia is not clear, although mineralocorticoid-induced renal resistance to the actions of AVP and disturbed osmoregulation of AVP release have been documented in a dog with primary hyperaldosteronism (Rijnberk et al, 2001). Similar abnormalities have been identified in dogs with glucocorticoid excess, suggesting similar mechanisms of action for the polyuria and polydipsia in hyperaldosteronism and hyperadrenocorticism. Hyperaldosteronism-induced hypokalemia may also result in downregulation of aquaporin-2 water channels and urea transporters, thereby interfering with the ability to concentrate urine (Robben et al, 2006; Sands and Bichet, 2006). Baseline plasma aldosterone concentrations are markedly increased, and plasma renin activity is suppressed (see Chapters 10 and 11).

Pyelonephritis

Infection and inflammation of the renal pelvis can destroy the countercurrent mechanism in the renal medulla and the collecting ducts, resulting in isosthenuria, polyuria, polydipsia, and eventually renal failure. Bacterial endotoxins, especially those associated with *E. coli*, can also compete with AVP for its binding sites on the renal tubular membrane, causing a potentially reversible renal tubular insensitivity to AVP. A dog or cat with acute bacterial pyelonephritis may develop nonspecific systemic signs of lethargy, anorexia, and fever, and a neutrophilic leukocytosis may be identified on a CBC. Systemic signs are usually not present with chronic pyelonephritis. Pyelonephritis should also be suspected in a patient with recurring urinary tract infection. Urinalysis may reveal white blood cells and white blood cell casts, bacteria, and occasionally red blood cells. Culture of urine obtained by antepubic cystocentesis should be positive for bacterial growth. Abdominal ultrasonography and excretory urography may reveal abnormalities consistent with pyelonephritis (e.g., renal pelvis dilatation).

Hypokalemia

Hypokalemia is believed to render the terminal portion of the nephron less responsive to AVP by causing downregulation of aquaporin-2 water channels, thereby interfering with the ability to concentrate urine (Robben et al, 2006; Sands and Bichet, 2006). Hypokalemia may also alter the hypertonic medullary interstitial gradient by causing downregulation of urea transporters and interfering with solute accumulation and may interfere with release of AVP from the pituitary. Polyuria and polydipsia are not common clinical signs of hypokalemia. The most common clinical signs are related to neuromuscular dysfunction of skeletal, cardiac, and smooth muscle (e.g., weakness, cervical ventriflexion). Hypokalemia usually develops secondary to another disorder, many of which also cause polyuria and polydipsia.

Hypoadrenocorticism (Addison's Disease)

Adrenocortical insufficiency results in impaired ability to concentrate urine (see Chapter 12). Despite normal kidney function and severe hypovolemia, many dogs with hypoadrenocorticism have a urine specific gravity of less than 1.030 and in some dogs urine specific gravity is in the isosthenuric range. Mineralocorticoid deficiency results in chronic sodium wasting, renal medullary solute washout, and loss of the medullary hypertonic gradient. Adrenalectomy in rats also decreases AVP-stimulated activation of renal medullary adenylate cyclase, primarily because of impairment in the coupling between the AVP receptor complex and adenylate cyclase. Treatment with dexamethasone corrects the defect. Hypercalcemia occurs in some patients with hypoadrenocorticism and may also play a role in the generation of polyuria and polydipsia.

Polyuria and polydipsia typically develop early in the course of the disease and are quickly overshadowed by the more worrisome and obvious vomiting, diarrhea, anorexia, weakness, and lethargy seen in these patients, although occasionally polyuria and polydipsia are the primary owner complaints. The polyuria of hypoadrenocorticism can be difficult to differentiate from primary renal failure unless specific tests of the pituitary adrenocortical axis (e.g., ACTH stimulation test) are performed. Initial suspicion for hypoadrenocorticism usually follows evaluation of serum electrolytes, although hyperkalemia and hyponatremia can also occur with renal insufficiency.

Hyperthyroidism. Polyuria and polydipsia are common findings in cats and dogs with hyperthyroidism. The exact mechanism for the polyuria and polydipsia is not clear. Increased renal medullary blood flow may decrease medullary hypertonicity and impair water resorption from the distal portion of the nephron. Psychogenic polydipsia secondary to thyrotoxicosis and, in some patients, concurrent renal insufficiency may also contribute to the polyuria and polydipsia. The tentative diagnosis of hyperthyroidism is usually based on clinical signs, palpation of an enlarged thyroid lobe or lobes (i.e., goiter), and measurement of serum thyroxine (T_4) concentration.

Acromegaly

Excessive secretion of growth hormone (GH) in the adult dog or cat results in acromegaly (see Chapter 2). Acromegaly causes carbohydrate intolerance and the eventual development of overt diabetes mellitus. In most cats and dogs with acromegaly, the polyuria is assumed to be caused by an osmotic diuresis induced by glycosuria. Renal insufficiency from a diabetic or GH-induced glomerulonephropathy may also play a role (Peterson et al, 1990).

Polycythemia

Polyuria and polydipsia may occur with polycythemia. Studies in two dogs with secondary polycythemia identified an increased osmotic threshold for AVP release, resulting in a delayed AVP response to increasing plasma osmolality (van Vonderen et al, 1997a). The authors attributed the abnormal AVP response to increased blood volume and hyperviscosity, which stimulate atrial natriuretic peptide (ANP) secretion and atrial and carotid bifurcation baroreceptors. ANP inhibits AVP release from the pituitary gland and the renal collecting duct's responsiveness to AVP (Dillingham and Anderson, 1986; Lee et al, 1987).

Primary and Psychogenic Polydipsia

Primary polydipsia is defined as a marked increase in water intake that cannot be explained as a compensatory mechanism for excessive fluid loss. In humans, primary polydipsia results from a defect in the thirst center or may be associated with mental illness (Reeves et al, 1998). Primary dysfunction of the thirst center resulting in compulsive water consumption has not been reported in the dog or cat, although an abnormal vasopressin response to hypertonic saline infusion has been reported in dogs with suspected primary polydipsia (van Vonderen et al, 1999). A psychogenic or behavioral basis for compulsive water consumption does occur in the dog but has not been reported in the cat. Psychogenic polydipsia may be induced by concurrent disease (e.g., hepatic insufficiency, hyperthyroidism) or may represent a learned behavior following a change in the pet's environment. Polyuria is compensatory to prevent overhydration. Psychogenic polydipsia is diagnosed by exclusion of other causes of polyuria and polydipsia and by demonstrating that the dog or cat can concentrate urine to a specific gravity in excess of 1.030 after water deprivation. This syndrome

BOX 1-1	Drugs and Hormones Causing Polyuria and Polydipsia in Dogs and Cats

Anticonvulsants*
    Phenobarbital
    Primidone
    Dilantin
Glucocorticoids*
Desoxycorticosterone pivalate (DOCP)*
Diuretics*
Mannitol
Synthetic thyroid hormone supplements
Amphotericin B
Lithium
Methoxyflurane
Sodium bicarbonate
Salt Supplementation*
Vitamin D (toxicity)

*Common cause

is discussed in more detail in subsequent sections (see Primary or Psychogenic Polydipsia later in this chapter).

Iatrogenic (Drug-Induced) Causes of Polydipsia and Polyuria

Several drugs have the potential to cause polyuria and polydipsia (Box 1-1). The most commonly encountered in small animal veterinary practice are glucocorticoids, diuretics, anticonvulsants (e.g., phenobarbital), synthetic levothyroxine, and salt supplementation. Drug-induced polyuria and polydipsia do not usually pose a diagnostic challenge. The polyuria and polydipsia should resolve following discontinuation of the drug; the time to resolution being dependent on the duration of action of the drug (e.g., prednisone versus long-acting depot glucocorticoid preparation). If polyuria and polydipsia persist, a concurrent disorder causing polyuria and polydipsia or renal medullary solute washout should be considered.

Renal Medullary Solute Washout

Loss of renal medullary solutes, most notably sodium and urea, results in loss of medullary hypertonicity and impaired ability of the nephron to concentrate the ultrafiltrate. Renal medullary solute washout is usually caused by one of the disorders previously described. It has also been associated with chronic diuretic therapy and abnormalities in circulation, such as hyperviscosity syndromes (polycythemia, hyperproteinemia), renal lymphatic obstruction (lymphosarcoma, lymphangiectasia), and systemic vasculitis (septicemia, systemic lupus erythematosus). Perhaps the most important clinical ramification of renal medullary solute washout is its potential to interfere with results of the modified water deprivation test (see Misdiagnosis [Inaccuracies] Using the Modified Water Deprivation Test). Hypertonicity of the renal medulla is usually restored once the underlying cause of the polyuria and polydipsia is corrected.

DIAGNOSTIC APPROACH TO POLYURIA AND POLYDIPSIA

Depending on the cause, the cost and time expenditure for evaluating a dog or cat with polyuria and polydipsia may be brief and inexpensive (e.g., diabetes mellitus) or time-consuming and costly

| TABLE 1-3 | URINALYSIS RESULTS IN DOGS WITH SELECTED DISORDERS CAUSING POLYURIA AND POLYDIPSIA |

| DISORDER | NUMBER OF DOGS | Urine Specific Gravity | | PROTEINURIA | WBC (> 5/HPF) |
		MEAN	RANGE		
CDI	20	1.005	1.001-1.012	5%	0%
Psychogenic polydipsia	18	1.011	1.003-1.023	0%	0%
Hyperadrenocorticism	20	1.012	1.001-1.027	48%	0%
Renal insufficiency	20	1.011	1.008-1.016	90%	25%
Pyelonephritis	20	1.019	1.007-1.045	70%	75%

CDI, Central diabetes insipidus; *HPF,* high power field; *WBC,* white blood count.

(e.g., partial CDI). Therefore, the clinician should be reasonably sure that polyuria and polydipsia exist, preferably based on a combination of history, multiple random urine specific gravity determinations, and if necessary, quantitation of water consumption over several days with the dog or cat in the home environment. In dogs, normal water intake is usually less than 80 mL/kg of body weight/24 h. Water intake between 80 and 100 mL/kg/24 h is suggestive of polydipsia but may be normal in some dogs. Water intake greater than 100 mL/kg/24 h confirms polydipsia. Similar values are used for cats, although most cats drink considerably less than these amounts. If an owner knows the volume of water the pet is consuming in an average 24-hour period and if that amount exceeds the upper limit of normal, a diagnostic evaluation to determine the cause is warranted. If 24-hour water intake is normal, pathologic polyuria and polydipsia are unlikely and another inciting factor (e.g., hot weather) should be sought, or misinterpretation of polyuria (e.g., pollakiuria instead of polyuria) should be considered. If the owner is certain that a change in the volume of water consumption or urination exists, even though water consumption is still in the normal range, a diagnostic evaluation may still be warranted.

Assessment of urine specific gravity may be helpful in identifying polyuria and polydipsia and may provide clues to the underlying diagnosis, especially if multiple urine specific gravities are evaluated (Table 1-3). Urine specific gravity varies widely among healthy dogs and, in some dogs, can range from 1.006 to greater than 1.040 within a 24-hour period (van Vonderen et al, 1997b). Wide fluctuations in urine specific gravity have not been reported in healthy cats.

We prefer to have the owner collect several urine samples at different times of the day for 2 to 3 days, storing the urine samples in the refrigerator until they can be brought to the veterinary hospital for determination of urine specific gravity. Urine specific gravities measured from multiple urine samples that are consistently less than 1.020 support the presence of polyuria and polydipsia and the need for a diagnostic evaluation to determine the cause; the lower the urine specific gravities, the stronger the support for the existence of a polyuria/polydipsia disorder. Identification of one or more urine specific gravities greater than 1.030 supports normal urine concentrating ability and an intact, functioning pituitary vasopressin-renal tubular cell axis. Dogs and cats may still have polyuria and polydipsia despite identification of concentrated urine; possible differential diagnoses include disorders causing an osmotic diuresis (e.g., diabetes mellitus), psychogenic polydipsia, and disorders in the regulation of AVP secretion (van Vonderen et al, 1999).

Many potential causes exist for the development of polyuria and polydipsia in dogs and cats (see Table 1-2), one of the least common being diabetes insipidus. An animal with a history of severe polyuria and polydipsia should be thoroughly evaluated for other causes of polyuria and polydipsia prior to performing specific diagnostic procedures for diabetes insipidus or psychogenic polydipsia (Fig. 1-7). Our diagnostic approach to the animal with polyuria and polydipsia is initially to rule out the more common causes. In the dog, these include chronic renal failure, diabetes mellitus, hyperadrenocorticism, liver insufficiency, and hypercalcemia. In the cat, these include chronic renal failure, diabetes mellitus, and hyperthyroidism. Recommended initial diagnostic studies include a CBC, serum biochemistry panel, and urinalysis with bacterial culture of urine obtained by antepubic cystocentesis. A serum T_4 concentration should be measured in older cats. Depending on the history and physical examination findings, abdominal ultrasonography may be warranted to evaluate the liver, kidneys, adrenal glands, and uterus or uterine stump in the female dog. Careful evaluation of the history, physical examination findings, and results of initial blood, urine, and diagnostic imaging results usually provides the diagnosis outright (e.g., diabetes mellitus, pyometra) or offers clues that allow the clinician to focus on the underlying cause (e.g., increased serum alkaline phosphatase and cholesterol in hyperadrenocorticism, hypercalcemia of malignancy).

Occasionally, the physical examination and initial data base are normal in the dog and, less commonly, the cat with polyuria and polydipsia. Viable possibilities in these dogs include diabetes insipidus, psychogenic water consumption, hyperadrenocorticism, renal insufficiency without azotemia, and possibly mild hepatic insufficiency and the early stages of hypoadrenocorticism. Viable possibilities in cats include renal insufficiency without azotemia, mild hepatic insufficiency, and diabetes insipidus. Hyperadrenocorticism, renal insufficiency, and hepatic insufficiency should be ruled out before performing tests to establish a diagnosis of diabetes insipidus or psychogenic polydipsia. Diagnostic tests to consider include tests of the pituitary adrenocortical axis, liver function tests (e.g., pre- and postprandial bile acids), urine protein-to-creatinine ratio, endogenous or exogenous creatinine clearance studies, contrast imaging of the kidney, and, if indicated, renal biopsy.

Careful evaluation of urine specific gravity and urine protein loss may provide clues to the underlying diagnosis (see Table 1-3). For example, if the urine specific gravity measured on multiple urine samples is consistently in the isosthenuric range (1.008 to 1.015), renal insufficiency should be considered the primary differential diagnosis, especially if the BUN and serum creatinine concentration are high normal or increased (i.e., ≥ 25 mg/dL and ≥ 1.6 mg/dL, respectively) and proteinuria is present. Although isosthenuria is relatively common in dogs with hyperadrenocorticism,
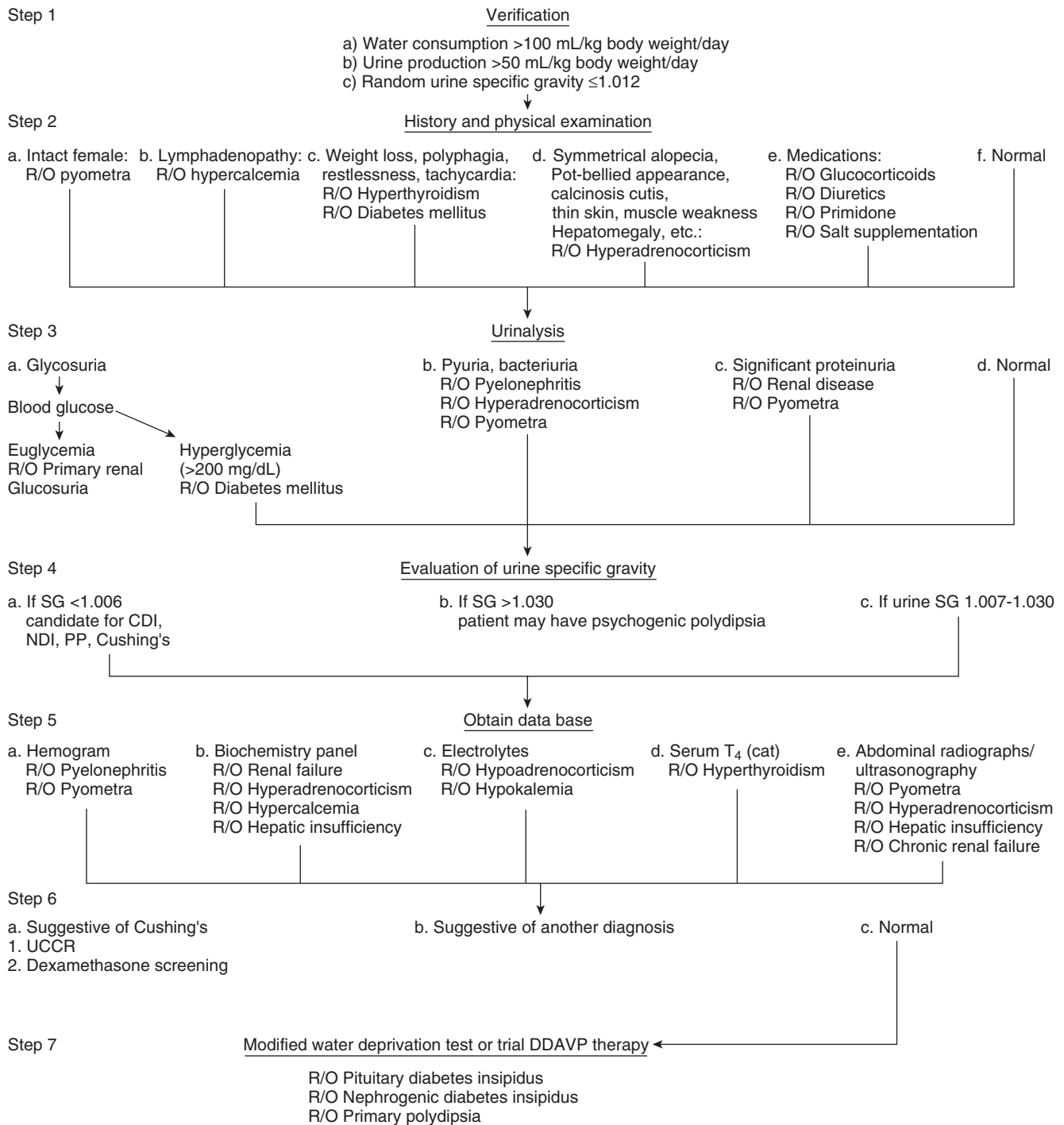
Step 1 — Verification

a) Water consumption >100 mL/kg body weight/day
b) Urine production >50 mL/kg body weight/day
c) Random urine specific gravity ≤1.012

Step 2 — History and physical examination

a. Intact female: R/O pyometra

b. Lymphadenopathy: R/O hypercalcemia

c. Weight loss, polyphagia, restlessness, tachycardia: R/O Hyperthyroidism R/O Diabetes mellitus

d. Symmetrical alopecia, Pot-bellied appearance, calcinosis cutis, thin skin, muscle weakness Hepatomegaly, etc.: R/O Hyperadrenocorticism

e. Medications: R/O Glucocorticoids R/O Diuretics R/O Primidone R/O Salt supplementation

f. Normal

Step 3 — Urinalysis

a. Glycosuria → Blood glucose → Euglycemia R/O Primary renal Glucosuria / Hyperglycemia (>200 mg/dL) R/O Diabetes mellitus

b. Pyuria, bacteriuria R/O Pyelonephritis R/O Hyperadrenocorticism R/O Pyometra

c. Significant proteinuria R/O Renal disease R/O Pyometra

d. Normal

Step 4 — Evaluation of urine specific gravity

a. If SG <1.006 candidate for CDI, NDI, PP, Cushing's

b. If SG >1.030 patient may have psychogenic polydipsia

c. If urine SG 1.007-1.030

Step 5 — Obtain data base

a. Hemogram R/O Pyelonephritis R/O Pyometra

b. Biochemistry panel R/O Renal failure R/O Hyperadrenocorticism R/O Hypercalcemia R/O Hepatic insufficiency

c. Electrolytes R/O Hypoadrenocorticism R/O Hypokalemia

d. Serum T_4 (cat) R/O Hyperthyroidism

e. Abdominal radiographs/ ultrasonography R/O Pyometra R/O Hyperadrenocorticism R/O Hepatic insufficiency R/O Chronic renal failure

Step 6

a. Suggestive of Cushing's
1. UCCR
2. Dexamethasone screening

b. Suggestive of another diagnosis

c. Normal

Step 7 — Modified water deprivation test or trial DDAVP therapy ←

R/O Pituitary diabetes insipidus
R/O Nephrogenic diabetes insipidus
R/O Primary polydipsia

FIGURE 1-7 The diagnostic plan in a dog or cat with severe polydipsia and polyuria. *CDI,* Central diabetes insipidus; *DDAVP,* desmopressin acetate; *NDI,* nephrogenic diabetes insipidus; *PP,* primary (psychogenic) polydipsia; *R/O,* rule out (a diagnosis); *SG,* specific gravity; T_4, thyroxine; *UCCR,* urinary cortisol creatinine ratio.

psychogenic water consumption, hepatic insufficiency, pyelonephritis, and partial CDI with concurrent water restriction, urine specific gravities tend to fluctuate above (hyperadrenocorticism, hypoadrenocorticism, psychogenic water consumption, hepatic insufficiency, pyelonephritis) and below (hyperadrenocorticism, hepatic insufficiency, psychogenic water consumption, partial CDI) the isosthenuric range in these disorders. In contrast, if the urine specific gravity is consistently less than 1.006, renal insufficiency is ruled out and central and primary NDI, psychogenic water consumption, hyperadrenocorticism and hepatic insufficiency should

be considered the primary differential diagnoses. CDI and primary NDI are ruled out if the urine specific gravity exceeds 1.025. Urine specific gravities that range from less than 1.005 to greater than 1.030 are suggestive of psychogenic polydipsia.

All realistic causes of secondary acquired NDI should be ruled out before performing tests (especially the modified water deprivation test) to diagnose CDI, primary NDI and psychogenic polydipsia. An index of suspicion for CDI and primary NDI versus psychogenic polydipsia can often be gained after reviewing the history and findings on physical examination and routine blood
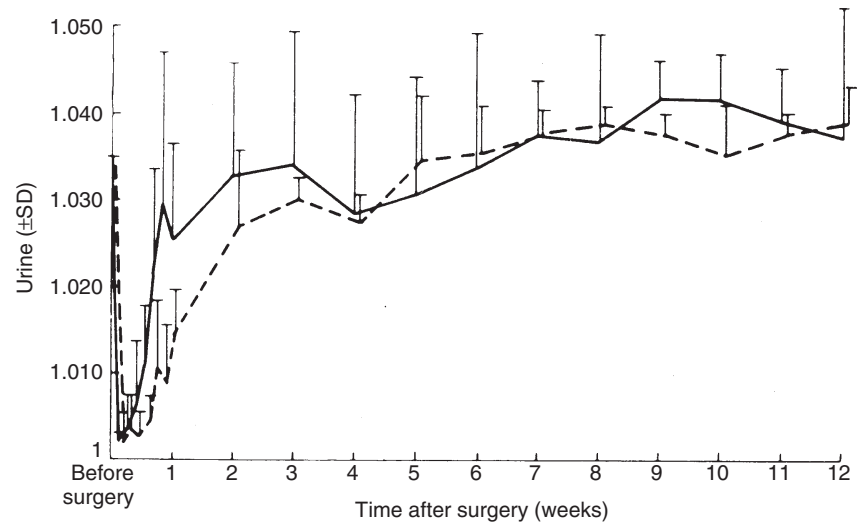
FIGURE 1-8 Mean urine specific gravity obtained before and for 3 months after hypophysectomy in four dogs treated with intraoperative polyionic fluids *(solid line)* and four dogs treated with intraoperative polyionic fluids and dexamethasone *(dashed line).* (From Lantz GC, et al: Transsphenoidal hypophysectomy in the clinically normal dog, *Am J Vet Res* 49[7]:1134-1142, 1988.)

and urine tests. CDI and primary NDI are polyuric disorders with compensatory polydipsia to minimize dehydration. The presence of neurologic signs, serum sodium concentrations at the upper limit of the reference range, urine specific gravities consistently in the hyposthenuric range, and rapid onset of dehydration with water restriction support the presence of CDI or primary NDI. In contrast, psychogenic polydipsia is a polydipsic disorder with compensatory polyuria to prevent water intoxication. The identification of behavioral issues in the dog, serum sodium concentrations at the lower limit of the reference range, urine specific gravities that fluctuate below and above the isosthenuric range, and a relatively prolonged time interval to develop dehydration after water restriction support the presence of psychogenic polydipsia. The definitive diagnosis of CDI, primary NDI and psychogenic water consumption should be based on results of the modified water deprivation test, measurement of plasma osmolality, and response to synthetic vasopressin therapy (see Confirming the Diagnosis of Diabetes Insipidus).

ETIOLOGY OF DIABETES INSIPIDUS AND PRIMARY POLYDIPSIA

Vasopressin Deficiency—Central Diabetes Insipidus

Definition

CDI is a polyuric syndrome that results from a lack of sufficient AVP to concentrate the urine for water conservation. This deficiency may be absolute or partial. An absolute deficiency of AVP causes persistent hyposthenuria and severe diuresis. Urine specific gravity in dogs and cats with complete lack of AVP remains hyposthenuric (≤ 1.006), even with severe dehydration. A partial deficiency of AVP, referred to as a *partial CDI,* also causes persistent hyposthenuria and a marked diuresis as long as the dog or cat has unlimited access to water. During periods of water restriction, however, dogs and cats with partial CDI can increase their urine specific gravity into the isosthenuric range (1.008 to 1.015) but cannot typically concentrate their urine above 1.015 to 1.020, even with severe dehydration. For any dog or cat with partial CDI, maximum urine-concentrating ability during dehydration is inversely related to the severity of the deficiency in AVP secretion; that is, the more severe the AVP deficiency, the less concentrated the urine specific gravity during dehydration.

Pathophysiology

Destruction of the production sites for vasopressin—the supraoptic and paraventricular nuclei of the hypothalamus—and/or loss of the major ducts (axons) that carry AVP to the storage and release depots in the posterior pituitary (see Fig. 1-2) result in CDI. Permanent CDI requires an injury that is sufficiently high in the neurohypophyseal tract to cause bilateral neuronal degeneration in the supraoptic and paraventricular nuclei. Transection of the hypothalamic hypophyseal tract below the median eminence or removal of the posterior lobe of the pituitary usually causes transient (albeit severe) CDI and polyuria because sufficient hormone can be released from fibers ending in the median eminence and pituitary stalk to prevent occurrence of permanent diabetes insipidus (Fig. 1-8; Ramsay, 1983).

Etiology

CDI may result from any condition that damages the neurohypophyseal system. Recognized causes for CDI in the dog and cat are listed in Box 1-2. Idiopathic cases of CDI are the most common, appearing at any age in any breed in either gender. Necropsies performed in dogs and cats with idiopathic CDI fail to identify an underlying reason for the AVP deficiency.

Autoimmune hypothalamitis has been suggested as a possible cause of idiopathic CDI in humans (Salvi et al, 1988). Circulating AVP cell antibodies, which bind to cell membranes of hypothalamic preparations, have been identified in some humans with CDI (Scherbaum, 1987). AVP cell antibodies have been identified prior to the development of CDI, and titers of AVP cell antibodies decline eventually to negative values with increasing duration of the disease (Bhan and O'Brien, 1982; Scherbaum et al, 1986). These patients also show a significant association with other endocrine disorders (e.g., immune thyroiditis, Addison's disease), suggesting that, at least in some cases, polyendocrine autoimmunity may also involve the hypothalamus (see Chapter 3). A similar association between CDI and other endocrinopathies has not been identified in dogs and cats. However, lymphocytic hypophysitis has been documented in a dog with CDI, an inflammatory mass compressing the hypothalamus, and marked lymphocytic infiltration of the adenohypophysis (Meij et al, 2012). In humans, lymphocytic inflammation involving the posterior pituitary lobe and infundibulum is called *lymphocytic infundibuloneurohypophysitis* and humans typically develop acute onset of diabetes insipidus with intracranial mass-effect symptoms (Abe, 2008).

BOX 1-2	Recognized Causes of Central Diabetes Insipidus in Humans, Dogs, and Cats

Humans	Dogs/Cats
Acquired	**Acquired**
Idiopathic	Idiopathic
Head trauma	Head trauma
Neoplasia	Neoplasia
Craniopharyngioma	Craniopharyngioma
Germinoma	Chromophobe adenoma and
Meningioma	adenocarcinoma
Lymphoma	Meningioma
Leukemia	Metastases
Adenoma	Hypothalamic/pituitary malformation
Metastases	Cysts
Granulomatous disease	Inflammation (lymphocytic hypophysitis)
Infectious	Parasite migration
Viral	Transsphenoidal hypophysectomy
Bacterial (abscess)	
Vascular	**Familial (?)**
Sheehan syndrome	
Aneurysms	
Immune-mediated	
Lymphocytic infundibulohypophysitis	
Hypophysectomy	
Familial	

FIGURE 1-9 Transverse **(A)** and sagittal **(B)** magnetic resonance images of the pituitary region in a 12-year-old male Boxer with central diabetes insipidus (CDI), hypothyroidism, and neurologic signs. A mass is evident in the region of the pituitary gland, hypothalamus, and rostral floor of the calvarium *(arrows)*.

The most common identifiable causes for CDI in dogs and cats are head trauma (accidental or neurosurgical), neoplasia, and hypothalamic/pituitary malformations (e.g., cystic structures). Head trauma may cause transient or permanent CDI, depending on the viability of the cells in the supraoptic and paraventricular nuclei. Trauma-induced transection of the pituitary stalk often results in transient CDI, usually lasting 1 to 3 weeks (see Fig. 1-8; Lantz et al, 1988; Authement et al, 1989). The duration of diabetes insipidus depends on the location of the transection of the hypophyseal stalk relative to the hypothalamus. Transection at more proximal levels, close to the median eminence, is associated with a longer time for hypothalamic axons to undergo regeneration and secretion of AVP. Trauma-induced CDI should be suspected when severe polydipsia and polyuria develop within 48 hours of head trauma or when hypernatremia, hyposthenuria, and hypertonic dehydration develop in a traumatized dog or cat that is being treated with IV fluids rather than water ad libitum (see Complications of the Modified Water Deprivation Test: Hypertonic Dehydration and Hypernatremia later in this chapter).

Transient or permanent diabetes insipidus commonly occurs following transsphenoidal hypophysectomy for the treatment of pituitary-dependent hyperadrenocorticism in dogs. In one study evaluating hypophysectomy in 127 dogs with pituitary-dependent hyperadrenocorticism, postoperative CDI was transient in 78% of the dogs with DDAVP discontinued 2 weeks after surgery in 47% and eventually discontinued in 31% a median of 133 days (range, 28 to 1329 days) postsurgery (Hanson et al, 2005). CDI was present until death or until latest available follow-up in 22% of the dogs. In another study, the incidence of postoperative permanent CDI in dogs undergoing transsphenoidal surgery for Cushing's disease was strongly influenced by the size of the pituitary tumor; the larger the tumor, the more likely CDI was permanent after surgery (Teshima et al, 2011).
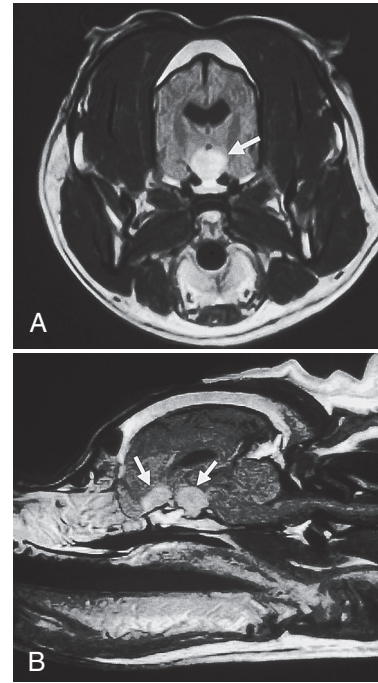
Neoplastic destruction of magnocellular neurons may also cause CDI. However, 90% of the magnocellular neurons must be destroyed to produce symptomatic diabetes insipidus. To produce CDI, a mass lesion would have to destroy a large area of the hypothalamus or be located where the tracks of the nuclei converge at the base of the hypothalamus and the top of the pituitary stalk (Robinson and Verbalis, 2011). Tumors confined to the sella do not cause CDI. Primary intracranial tumors associated with diabetes insipidus in dogs and cats include craniopharyngioma, pituitary chromophobe adenoma, and pituitary chromophobe adenocarcinoma (Fig. 1-9; Neer and Reavis, 1983; Goossens et al, 1995; Harb et al, 1996). Tumor metastases to the hypothalamus and pituitary gland can also cause CDI. In humans, metastatic tumors most often spread from the lung or breast (Reeves et al, 1998). Metastatic mammary carcinoma, lymphoma, malignant melanoma, and pancreatic carcinoma have been reported to cause CDI by their presence in the pituitary gland and hypothalamus in dogs (Capen and Martin, 1983; Davenport et al, 1986). Metastatic neoplasia as a cause for CDI has not yet been reported in the cat.

A rare, hereditary form of CDI occurs in humans, is transmitted as an autosomal dominant trait, has equal occurrence in males and females, displays father-to-son transmission, and shows variable expression among affected individuals (Baylis and Robertson, 1981). This condition is believed to result from a degenerative disorder affecting the magnocellular neurons (Kaplowitz et al, 1982). Although CDI is well documented in kittens and puppies, hereditary CDI has not yet been documented. In one report, hereditary CDI was suggested in two sibling Afghan Hound pups that developed CDI at younger than 4 months of age and were from a bitch suffering from polyuria and polydipsia "all her life" (Post et al, 1989). Necropsy of these puppies revealed vacuolated areas in the neurohypophysis and hypothalamohypophysial tracts of the median eminence of the tuber cinereum, findings that suggested

hypomyelination or demyelination. We have also diagnosed CDI in a litter of five 8-week-old German Short-Haired Pointers and three of five 7-week-old Schnauzers, suggesting possible familial CDI in these dogs.

Primary Nephrogenic Diabetes Insipidus

Definition

NDI is a polyuric disorder that results from impaired responsiveness of the nephron to the actions of AVP. Plasma AVP concentrations are normal or increased in animals with this disorder. NDI is classified as primary or secondary (acquired). Secondary or acquired NDI is common in dogs and cats and is discussed in an earlier section (see Acquired [Secondary] Nephrogenic Diabetes Insipidus). Primary NDI is a rare disorder in dogs and cats; polydipsia and polyuria typically become apparent by the time the dog or cat is 8 to 12 weeks of age suggesting that primary NDI may be a congenital disorder.

Etiology

Two types of congenital NDI have been identified in humans: mutations of the V_2 receptor and mutations of the aquaporin-2 water channels (van Lieburg et al, 1999; Bichet, 2006). More than 90% of cases of congenital NDI in humans are X-linked recessive disorders in males who have one of more than 200 different mutations of the V_2 receptor (Spanakis et al, 2008). When congenital NDI is identified in a girl, it is likely that the defect is a mutation of the aquaporin-2 water channel gene producing an autosomal recessive disease (Sands and Bichet, 2006). For both disorders, clinical signs are apparent shortly after birth. The diagnosis of congenital NDI is established by high concentrations of AVP in the presence of hypotonic polyuria and the lack of response to DDAVP administration.

Only a few reports of primary NDI in dogs have appeared in the veterinary literature (Breitschwerdt et al, 1981; Grunbaum et al, 1990; Grunbaum and Moritz, 1991). Primary NDI has not yet been reported in the cat. The cause of primary NDI in dogs and cats is unknown. Electron microscopic examination of the renal medulla in a Miniature Poodle with primary NDI revealed vacuoles in the cells of the Henle loops, blood vessels, and interstitium, but the significance of these lesions is not known. Necropsy failed to identify any lesions in the kidney of a German Shepherd dog with primary NDI.

Familial NDI has been reported in a family of Huskies, in which the female parent was diagnosed as a carrier of the NDI gene, and three of four male puppies in her litter had NDI (Grunbaum et al, 1990). Affected puppies possessed normal V_2 receptor numbers in the kidney inner medulla, but the receptors had a ten-fold lower binding affinity for AVP than in normal dogs (Luzius et al, 1992). Adenylate cyclase stimulation by AVP was similarly reduced in a dose-response manner; however, stimulation of adenylate cyclase by non–AVP-mediated chemicals was comparable for normal and NDI-affected dogs, implying normal adenylate cyclase in the affected Huskies. The NDI-affected dogs also had antidiuretic responses to high doses of DDAVP, consistent with their possessing V_2 receptors of lower binding affinity.

In an older dog and cat, primary NDI should only be considered if polyuria and polydipsia has been present the animal's entire life. The onset of polyuria and polydipsia later in life in a dog or cat suspected to have NDI is suggestive of acquired NDI. A complete evaluation of the kidney, including creatinine clearance studies, IV pyelogram, computed tomographic (CT) or magnetic resonance imaging (MRI) scan, and kidney biopsy should be considered in these dogs and cats if another cause of for acquired NDI is not identified.

Primary and Psychogenic Polydipsia

Primary polydipsia (compulsive water consumption) is a syndrome characterized by ingestion of excess water resulting in compensatory polyuria to prevent water intoxication. In humans, primary polydipsia is most commonly found in individuals with underlying psychiatric illness (Cronin, 1987; Victor et al, 1989) and rarely, in individuals with lesions involving the thirst center. The cause of the polydipsia in individuals with psychiatric illness is uncertain, and most patients have, in addition to polydipsia, some abnormality in water excretion, such as excessive AVP secretion (Goldman et al, 1988).

Primary polydipsia caused by a hypothalamic lesion affecting the thirst center has not been reported in the dog or cat. A psychogenic basis for compulsive water consumption occurs uncommonly in the dog and has not been reported in the cat. Affected animals are usually hyperactive dogs that are placed in exercise-restrictive environments. Some of these dogs have had significant changes to their environment, resulting in unusual stress. In some dogs, compulsive water consumption is a learned behavior to gain attention from the owner. Dogs with psychogenic water consumption can concentrate urine to greater than 1.030 during water deprivation, although the latter may take hours because of concurrent renal medullary solute washout. Urine specific gravity may vary widely over time, and concentrated urine may be identified on random urine evaluation. Identification of concentrated urine implies hypothalamic AVP production, pituitary AVP secretion, and renal tubular responsiveness to AVP.

Abnormal AVP release in response to hypertonic saline stimulation was described in four dogs with suspected primary polydipsia (van Vonderen et al, 1999). All dogs presented for polyuria and polydipsia and had normal routine laboratory examinations except for hyposthenuria and concentrated urine during the water deprivation test. During serial measurements, urine osmolality spontaneously reached high concentrations (i.e., greater than 1000 mOsm/kg of H_2O) in two dogs. During water deprivation, plasma AVP concentrations remained relatively low in all dogs. The AVP response to hypertonic saline infusion was abnormal in all dogs, with an increased threshold value in three dogs, an increased sensitivity in two dogs, and an exaggerated response in one dog. These findings suggested a primary disturbance in the regulation of AVP secretion, although chronic overhydration may have caused downregulation of AVP release in response to hypertonicity (Moses and Clayton, 1993). Subnormal AVP release during water deprivation and hypertonic stimulation has been documented in humans with primary polydipsia (Zerbe and Robertson, 1981); these individuals were subsequently classified as having partial diabetes insipidus. It is not clear whether the dogs described by van Vonderen, et al., (1999) represent a variant or early stage of partial diabetes insipidus. They were classified as having primary polydipsia based on their ability to concentrate urine to a specific gravity greater than 1.030, but the identified abnormalities suggest a problem with AVP release rather than the thirst center, per se.

CLINICAL FEATURES OF DIABETES INSIPIDUS AND PSYCHOGENIC POLYDIPSIA

Signalment

Central Diabetes Insipidus

There is no apparent breed, gender, or age predilection for CDI (Fig. 1-10). Of 60 dogs diagnosed with CDI at University of
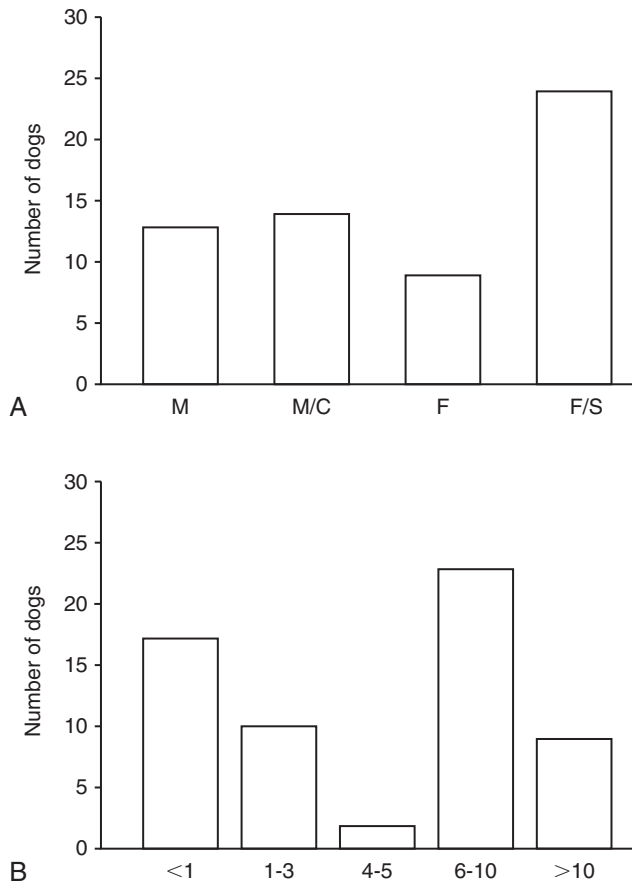
A

B

FIGURE 1-10 Gender **(A)** and age **(B)** distribution of 60 dogs diagnosed with central diabetes insipidus (CDI). *F*, Female; *F/S*, female/spayed; *M*, male; *M/C*, male/castrated.

FIGURE 1-11 Duration of polyuria and polydipsia in 38 dogs with central diabetes insipidus (CDI) before owners presented their pet to the veterinarian for examination.

California, Davis, 25 different breeds were represented. The Labrador Retriever (eight dogs), Boxer (five dogs), and German Shepherd (five dogs) were the breeds most commonly affected. The age at time of diagnosis in these 60 dogs ranged from 7 weeks to 14 years, with a median age of 6 years. Most dogs diagnosed with CDI were younger than 2 years or older than 5 years of age.

Twelve cats with CDI have been reported in the literature (Burnie and Dunn, 1982; Winterbotham and Mason, 1983; Kraus, 1987; Brown et al, 1993; Pittari, 1996; Aroch et al, 2005), and we have diagnosed an additional four cats at UC Davis. Thirteen of these sixteen cats were Domestic Short- or Long-Haired, two were Persian, and one was an Abyssinian. Eight of the cats were female or female/spayed, and eight were male or male/castrated. The age at the time of diagnosis of CDI ranged from 8 weeks to 6 years, with a mean of 1½ years.

Primary Nephrogenic Diabetes Insipidus

Primary NDI is rare in dogs and cats. To date, primary NDI has been reported in a 13-week-old male German Shepherd dog, an 18-month-old male Miniature Poodle, an 18-month-old female Boston Terrier, and a family of Huskies (Breitschwerdt et al, 1981; Grunbaum et al, 1990). We have also diagnosed NDI in a 5-month-old Norwegian Elkhound and a 1-year-old Boston Terrier. Both dogs had polyuria and polydipsia since being acquired by their owners at 6 to 8 weeks of age. Primary NDI has not yet been reported in the cat.
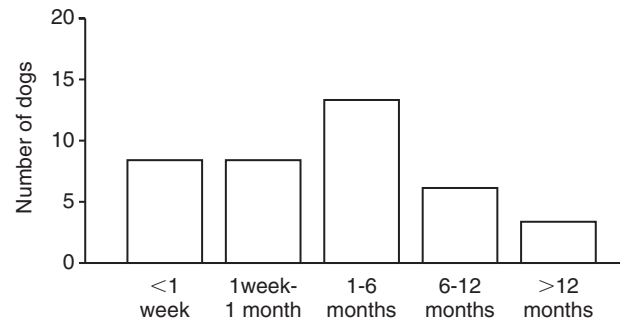
Psychogenic Polydipsia

Psychogenic polydipsia can be diagnosed in dogs of any age, either gender, and numerous breeds. Fifteen different breeds were represented in 18 dogs diagnosed with psychogenic polydipsia at UC Davis. Eleven dogs were female or female/spayed, and the age at time of diagnosis ranged from 6 months to 11 years, with a mean and median age of 4½ and 4 years, respectively. Psychogenic polydipsia has not yet been reported in the cat.

Clinical Signs

Polyuria and polydipsia are the hallmark clinical signs for diabetes insipidus and psychogenic polydipsia. Polyuria and polydipsia can be quite severe, with 24-hour water intake exceeding 200 mL/kg. Polyuria and polydipsia have usually been present for 1 to 6 months before veterinary care is sought (Fig. 1-11). Many owners also report urinary incontinence, in part because of the frequency of urination and loss of normal "house broken" behavior and in part because of the inability to maintain continence because of the large volume of urine being produced, especially when the dog or cat is sleeping. Owners of cats with diabetes insipidus also complain about the increased frequency of changing the litter, which often needs to be done two or three times a day. An insatiable desire for water may result in the consumption of any liquid, including ice, snow, and urine. Occasionally, the afflicted pet's strong desire for water overrides its normal appetite (i.e., they would rather drink than eat), resulting in weight loss.

Additional clinical signs depend, in part, on the underlying cause. Other historical abnormalities (e.g., vomiting, diarrhea, coughing) are usually not present in dogs or cats with congenital, idiopathic, or trauma-induced forms of diabetes insipidus. These pets are typically alert and playful and have normal exercise tolerance. However, dogs with acquired CDI secondary to a growing pituitary or hypothalamic neoplasm may develop additional signs related to the nervous system, including inappetence, stupor, disorientation, pacing, ataxia, seizures, and tremors (Harb et al, 1996). Neurologic signs may be present at the time CDI is diagnosed or, more typically, develop weeks to months after CDI is identified. In one study, 6 of 20 dogs with CDI developed neurologic signs from 2 weeks to 5 months (median, 1 month) after CDI was diagnosed (Harb et al, 1996). A tumor in the region of the hypothalamus and pituitary was identified by CT scan or necropsy in all six dogs. Neurologic signs may also develop secondary to hypertonic dehydration and severe hypernatremia.

Physical Examination

As with the history, the abnormalities found during the physical examination depend on the underlying cause. For most animals, the physical examination is unremarkable, although some dogs tend to be thin. Abnormalities of the cardiovascular, respiratory, gastrointestinal, and urogenital systems are usually absent. Animals with idiopathic or congenital diabetes insipidus are alert and active. Typically, as long as access to water is not restricted, hydration, mucous membrane color, and capillary refill time remain normal. The presence of neurologic abnormalities is variable in dogs and cats with trauma-induced CDI or neoplastic destruction of the hypothalamus and/or pituitary gland. Many of these animals have no perceptible neurologic alterations on physical examination. A few show mild to severe neurologic signs, including stupor, disorientation, ataxia, circling, and pacing.

Clinical Pathology Abnormalities

Complete Blood Count

The CBC in dogs and cats with CDI or NDI is usually unremarkable. The white blood cell count and differential are normal. The red blood cell count is normal or mildly increased. Polycythemia is not common and is the result of a mild, clinically imperceptible state of dehydration. Diabetes insipidus is a primary polyuric disorder with compensatory polydipsia, and affected dogs and cats are chronically, albeit mildly, fluid-depleted to stimulate the compensatory thirst response. Owners commonly tire of their pets' polyuria and polydipsia and begin restricting access to water, further exacerbating dehydration. Fluid depletion results in hemoconcentration with a mild increase in hematocrit, red blood cell count, and serum total protein concentration. The CBC in dogs with psychogenic polydipsia is rarely abnormal.

Urinalysis

Random urinalysis in dogs and cats with CDI, NDI, or psychogenic polydipsia typically reveals a urine specific gravity less than 1.006, with values of 1.001 and 1.002 occurring commonly (Fig. 1-12). The corresponding urine osmolality is usually less than 300 mOsm/kg. A urine specific gravity in the isosthenuric range (1.008 to 1.015) does not rule out diabetes insipidus (see Fig. 1-12) or psychogenic polydipsia (see Table 1-3), especially when the urine has been obtained after water is knowingly or inadvertently withheld (e.g., a long car ride and wait in the veterinary office). Dogs and cats with partial diabetes insipidus can concentrate their urine into the isosthenuric range if dehydrated. The remaining components of the urinalysis in these animals are usually normal.

Extremely dilute urine is not commonly seen in veterinary practice, being limited usually to animals with postobstructive diuresis, excessive IV fluid administration, diuretic use, and hyperadrenocorticism, as well as CDI, NDI, and psychogenic polydipsia. Although numerous disorders can result in polydipsia and polyuria (see Table 1-2), most of these disorders do not cause the severe polyuria suggested by remarkable depression in the specific gravity (< 1.005). Although we have seen animals that were polyuric owing to hypercalcemia, hypokalemia, pyometra, pyelonephritis, and other disorders, the degree of urine dilution is less dramatic and typically in the 1.006 to 1.020 range. However, even mild disturbances in the ability to concentrate urine, resulting in urine specific gravities of 1.008 to 1.015, often alter behavior sufficiently to allow an owner to realize the change.
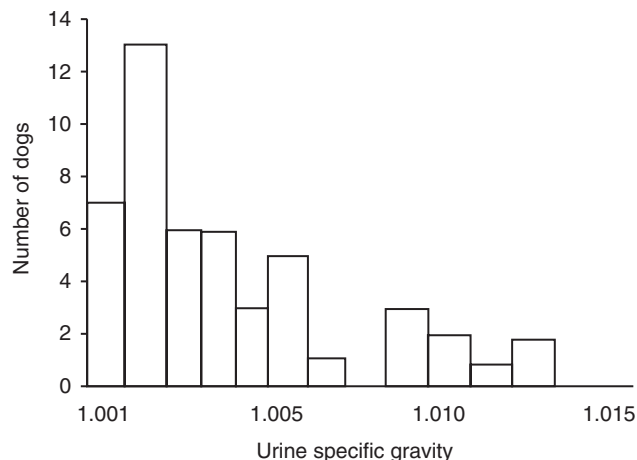

FIGURE 1-12 Urine specific gravity measured in 49 dogs with central diabetes insipidus (CDI) at the time of initial presentation to the veterinarian.

Serum Chemistries

The serum biochemistry panel is normal in most dogs and cats with diabetes insipidus and psychogenic polydipsia. The chronic and severe diuresis associated with CDI, NDI, and psychogenic polydipsia causes excessive loss of urea via the kidneys and may cause a subsequent reduction of BUN to concentrations of 5 to 10 mg/dL. Ten of 40 dogs with CDI had a BUN less than 10 mg/dL at the time of initial presentation to UC Davis. Inadequate access to water can cause severe dehydration and prerenal azotemia with hyposthenuria. The combination of prerenal azotemia, hypernatremia, and hyposthenuria was identified in 3 of our 40 dogs with CDI at the time of initial presentation to our hospital. These clinicopathologic abnormalities resolved after allowing the dogs to have access to water and initiating DDAVP therapy. Owners had restricted access to water in all three dogs.

Serum Electrolytes

Serum electrolytes are usually normal in dogs and cats with diabetes insipidus and psychogenic polydipsia. Mild hyponatremia and hypokalemia have been identified in 20% of our dogs with CDI and psychogenic polydipsia. More important, severe hypernatremia (serum sodium, 159 to 165 mEq/L) and hyperkalemia (5.4 to 5.9 mEq/L) have been identified in 15% of our dogs with CDI, abnormalities presumably developing secondary to water restriction and dehydration. An intact renin-angiotensin-aldosterone axis succeeds in maintaining electrolyte homeostasis in most dogs and cats despite the remarkable urine output associated with CDI, NDI, and psychogenic polydipsia. Maintenance of fluid and electrolyte balance depends on functioning thirst and hunger centers in the hypothalamus. Water restriction can cause severe dehydration in a matter of hours. Because free water diuresis continues despite water restriction, vascular and systemic hyperosmolarity develops. Increases in serum sodium contribute significantly to this hyperosmolarity. Hypertonic dehydration, severe hypernatremia, and neurologic signs may develop in a dog or cat with diabetes insipidus that is unable to drink (e.g., posttraumatic episode) or has restricted access to water (Reidarson et al, 1990). Severe hypernatremia is associated with significant metabolic consequences and is a difficult therapeutic challenge. Water deprivation studies to confirm the diagnosis of diabetes insipidus are not without complications and require careful patient monitoring to avoid dangerous consequences (see Complications of the Modified Water Deprivation Test: Hypertonic Dehydration and Hypernatremia).

CONFIRMING THE DIAGNOSIS OF DIABETES INSIPIDUS

Diagnostic tests to confirm and differentiate among CDI, primary NDI, and psychogenic water consumption include the modified water deprivation test, random plasma osmolality determination, and the clinical response of the dog or cat to DDAVP treatment. The results of these tests can be interpreted only after the causes for acquired NDI have been ruled out. Recommended initial diagnostic studies to rule out acquired NDI include a CBC; serum biochemistry panel; serum T_4 concentration (older cat); urinalysis with bacterial culture; abdominal ultrasonography; a urine cortisol-to-creatinine ratio, low-dose dexamethasone suppression test, or both in dogs; baseline serum cortisol concentration if hypoadrenocorticism is suspected (dogs); and pre- and postprandial bile acids if hepatic insufficiency is suspected. Results of these screening tests are normal in dogs and cats with CDI, primary NDI, and psychogenic water consumption, although a low-normal serum urea nitrogen concentration may be identified in animals with unrestricted access to water and erythrocytosis, hyperproteinemia, hypernatremia, and azotemia may be found if access to water has been restricted.

Pituitary-dependent hyperadrenocorticism can mimic CDI in the adult dog. Pituitary-dependent hyperadrenocorticism commonly causes severe polyuria and polydipsia and occasionally dogs have no other clinical signs, do not have the typical abnormalities (e.g., increased serum alkaline phosphatase activity, hypercholesterolemia) associated with the disease, and adrenal gland size is at the upper end of the reference interval with ultrasonography. Results of the modified water deprivation test in dogs with hyperadrenocorticism are similar to results in dogs with partial CDI (see Fig. 1-18) and, sometimes, dogs with psychogenic polydipsia. Severity of polyuria and polydipsia may improve noticeably to the owner after initiating treatment with DDAVP in these dogs but improvement tends to be transient, lasting only a few months, and the dog typically re-presents to the hospital with owner concerns that the DDAVP is no longer working. For these reasons, we always perform screening tests for hyperadrenocorticism (i.e., urine cortisol-to-creatinine ratio on urine collected at home; low dose dexamethasone suppression test) in an adult dog in which CDI and psychogenic polydipsia have risen to the top of the differential diagnoses and always before initiating DDAVP treatment.

An index of suspicion for CDI and primary NDI versus psychogenic polydipsia can often be gained after reviewing the history and findings on physical examination and routine blood and urine tests. The presence of neurologic signs or behavioral issues, the serum sodium concentration (i.e., upper versus lower limit of the reference range), the consistency of hyposthenuric urine, and the dog's susceptibility to dehydration after water restriction provide clues to the underlying diagnosis. The definitive diagnosis is based on results of the modified water deprivation test, measurement of plasma osmolality, measurement of plasma AVP concentration and response to synthetic vasopressin therapy.

Historically, the modified water deprivation test has been considered the best diagnostic test to differentiate between CDI, primary NDI and psychogenic polydipsia. However, the test can be labor-intensive, time-consuming, and expensive, especially if urine and plasma osmolalities and plasma AVP concentrations are measured. Results of the test can also be confusing, especially with partial deficiency syndromes. Currently, we consider performing a water deprivation test only in dogs (and rarely cats) that have a poor response to trial DDAVP treatment and when we suspect either partial CDI or psychogenic polydipsia. In these cases,

response to water deprivation provides insight into the animal's ability to concentrate urine (i.e., can the patient concentrate urine to a specific gravity above 1.030).

A simpler approach that is especially appealing in a busy practice is the evaluation of response to trial therapy with DDAVP and, if available, measurement of plasma osmolality obtained while the dog or cat has free access to water (see Random Plasma Osmolality as a Diagnostic Tool).

RESPONSE TO TRIAL THERAPY WITH DESMOPRESSIN ACETATE

CDI, primary NDI, and psychogenic polydipsia are uncommon to rare causes of polyuria and polydipsia in dogs and cats; and of these three differential diagnoses, partial CDI and psychogenic polydipsia are the most common. Because CDI is treated with DDAVP, a viable approach to establishing the diagnosis is to evaluate the animal's response to trial therapy with DDAVP (Aventis Pharmaceuticals). Oral DDAVP tablets or conjunctival drops of DDAVP nasal spray (see Treatment) should be administered every 12 hours for 7 days. The effect of DDAVP should not be critically evaluated until after 5 to 7 days of therapy because renal medullary solute washout may prevent a dog or cat with CDI from concentrating its urine and decreasing water intake after only 1 or 2 days of DDAVP treatment. Clients should notice a definite improvement in the severity of polyuria and polydipsia by the end of the treatment period if the polyuria and polydipsia are caused by CDI. Urine specific gravity should be measured on several urine samples collected by the client on the last couple of days of trial therapy. An increase in urine specific gravity by 50% or more, compared with pretreatment specific gravities, supports the diagnosis of CDI, especially if the urine specific gravity exceeds 1.030. There should be only minimal improvement in dogs and cats with primary NDI, although a response may be observed with very high doses of DDAVP (Luzius et al, 1992). Dogs and cats with psychogenic water consumption may exhibit a mild decline in urine output and water intake because the chronically low serum osmolality tends to depress AVP production. Theoretically, dogs with psychogenic polydipsia could develop clinical signs of hyponatremia during DDAVP therapy but we have not yet identified this complication (see Syndrome of Inappropriate Vasopressin Secretion: Excess Vasopressin). A thorough review of the diagnostic evaluation of the patient, owner compliance in treating the pet, and adjustments in the DDAVP treatment protocol should be undertaken in dogs and cats that fail to respond to DDAVP before considering the modified water deprivation test.

MODIFIED WATER DEPRIVATION TEST

Principle of the Test

The modified water deprivation test is designed to determine whether endogenous AVP is released in response to dehydration and whether the kidneys respond to this stimulus. The modified water deprivation test consists of two phases. In phase I the AVP secretory capabilities and renal distal and collecting tubule responsiveness to AVP are evaluated by assessing the effects of dehydration (i.e., water restriction until the animal loses 3% of its body weight) on urine specific gravity. The normal dog and cat, as well as those with psychogenic water consumption, should be able to concentrate urine to greater than 1.030 (1.035 in the cat) if dehydrated. Dogs and cats with partial and complete CDI and primary NDI have an impaired ability to concentrate urine in the face

of dehydration (Table 1-4 and see Figure 1-17). Phase II of the water deprivation test is indicated for dogs and cats that do not concentrate urine to greater than 1.030 during phase I of the test. Phase II determines the effect, if any, that exogenous AVP has on the renal tubular ability to concentrate urine in the face of dehydration (see Fig. 1-19). This phase differentiates impaired AVP secretion from impaired renal tubular responsiveness to AVP (see Table 1-4). The modified water deprivation test is not indicated to study the function of any organ system other than renal tubular response to AVP. This protocol is specifically contraindicated in patients suspected or known to have renal disease, those that are uremic owing to prerenal or primary renal disorders, and animals with suspected or obvious dehydration (see Approach if the Dog or Cat Is Brought into the Hospital Dehydrated).

Protocol

See Box 1-3.

Preparation for the Test

The severity of renal medullary solute washout is a difficult variable to evaluate in an animal with severe polydipsia and polyuria; yet it may have an effect on test results. Theoretically, correction of renal medullary solute washout improves renal tubular concentrating ability and the accuracy of the modified water deprivation test in differentiating among CDI, primary NDI, and psychogenic polydipsia. However, in animals with CDI, water restriction alone may not improve renal medullary solute washout; only after correction of polyuria and polydipsia with vasopressin therapy can the capacity of the renal tubule to concentrate urine be fully appreciated (Fig. 1-13). Nevertheless, we attempt to minimize the effects of severe medullary washout on the results of the modified water deprivation test, using progressive water restriction before initiating total water deprivation. The goal is to decrease 24-hour water intake to approximately 100 mL/kg the day prior to performing the water deprivation test. This goal can be hard to attain, especially in dogs or cats with severe polyuria and polydipsia. Total water intake per 24 hours should be determined by the owner and based on unrestricted access to water. Water restriction is begun once total 24-hour water intake has been quantified. We arbitrarily decrease daily water intake by 10% every 1 to 2 days and continue until the goal of 100 mL/kg/24 h is attained, the animal becomes aggressive for water, or begins to develop clinical signs suggestive of hypertonic dehydration (e.g., change in mentation; see Complications of the Modified Water Deprivation Test: Hypertonic Dehydration and Hypernatremia). Each day's 24-hour allotment of water should be divided into six to eight aliquots with the last aliquot given at bedtime. No food is given within 12 hours of beginning the test or during the procedure.

Phase I of the Test

The water deprivation test should always be started at the beginning of the workday, because animals undergoing this test must be observed and evaluated frequently. Most dogs and cats with CDI or primary NDI dehydrate and lose 3% of their body weight (end point for this phase of the test) within 3 to 10 hours (see Table 1-4). Withholding water and leaving the dog or cat with diabetes insipidus unattended for several hours or throughout the night may result in the development of severe complications and possibly death (see Complications of the Modified Water Deprivation Test: Hypertonic Dehydration and Hypernatremia). Frequent observation of the animal helps avoid complications or severe dehydration.
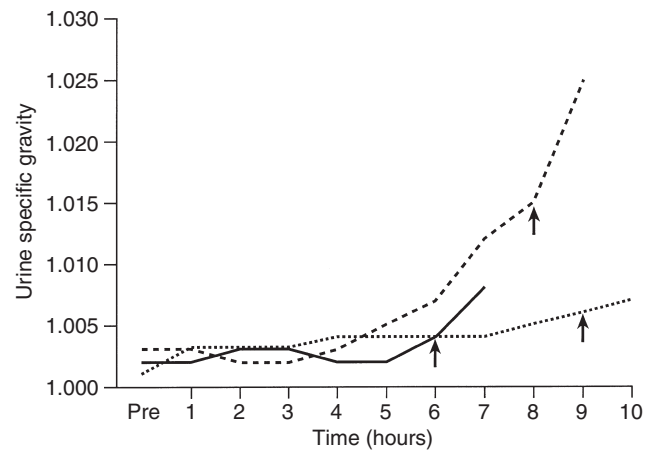

FIGURE 1-13 Results of the modified water deprivation test in a 1-year-old Persian cat with congenital central diabetes insipidus (CDI). *Solid line,* Initial water deprivation test results. *Dotted line,* Water deprivation test results after gradually restricting water consumption for 7 days prior to performing the test. *Dashed line,* Water deprivation test results after gradual water restriction and twice-daily injections of arginine vasopressin (AVP) for 7 days prior to performing the test. AVP injections were discontinued 24 hours prior to performing the test. ↑, 5% loss of body weight and aqueous AVP injection.

At the start of the test, the dog's or cat's bladder is emptied by micturition (walking outside) or catheterization; then an exact body weight is obtained and water is completely withheld from the patient. Urine specific gravity and, if possible, osmolality should be determined on a pretest urine sample. Periodic evaluation of BUN and serum sodium concentration, beginning at the start of the test, is helpful in identifying the development of azotemia or hypernatremia. The onset of azotemia or hypernatremia is a criterion for ending the test.

Although urine osmolality is more consistent and accurate than urine specific gravity, determination of urine specific gravity allows differentiation between CDI, primary NDI and psychogenic polydipsia in most situations, is readily available, inexpensive, and provides immediate information on urine concentration. Prior to starting the modified water deprivation test, the clinician should check the accuracy of the refractometer by ensuring that a reading of 1.000 is obtained with distilled water (Barsanti et al, 2000).

During Phase I of the Test

The urinary bladder should be emptied by micturition or catheterization every 1 to 2 hours. For cats, an indwelling urinary catheter is usually required. The specific gravity should be determined on each urine sample and an aliquot stored for osmolality determination, should it be desired at the end of the test. Most important, the dog or cat must be carefully weighed at least once an hour. Phase I ends when 3% of body weight has been lost or urine specific gravity exceeds 1.030. Additionally, the dog or cat should be assessed for clinical evidence of dehydration and changes in mentation or behavior. Periodic evaluation of BUN and serum sodium concentration should also be done. The test should be halted if the dog or cat becomes azotemic, hypernatremic, or severely dehydrated or develops changes in mentation or behavior.

End of Phase I

Maximal secretion of AVP and concentration of urine are achieved when an animal loses 3% of its body weight owing to loss of fluid

in the urine with simultaneous water deprivation. At that point the urinary bladder should be completely emptied, the urine checked for specific gravity and osmolality, and phase II of the water deprivation test initiated (see Box 1-3). If available, a plasma vasopressin concentration obtained at this time is helpful in interpreting the test (see Plasma Vasopressin Determinations).

Normal dogs typically require more than 24 hours to lose 3% of body weight following water deprivation. In contrast, water deprivation usually causes 3% or greater loss of body weight within 3 to 10 hours if the animal has CDI or primary NDI (see Table 1-4). Dogs or cats with partial CDI or psychogenic polydipsia may require considerably longer than 10 hours to achieve 3% loss of body weight. The clinician should always be prepared to continue the water deprivation test into the late evening hours. If this is not possible and the dog or cat has not yet lost 3% body weight or attained a urine specific gravity greater than 1.030 by the end of the working hours, the dog or cat can be transferred to a veterinary hospital with overnight care so the test can be continued.

Alternatively, the study can be stopped and water offered, initially in small amounts to prevent overzealous intake. The modified water deprivation test can then be repeated in a few days with the following adjustments in protocol: body weight is measured and water withheld beginning at midnight; the dog or cat is kept in a cage (or at home) for the remainder of the night, ideally with periodic visual assessment by individuals working at night (or by the owner if the patient is at home); the urinary bladder is completely emptied first thing in the morning and urine specific gravity and/or osmolality are measured; body weight is recorded; and phase I is continued as previously discussed. With this modification, the clinician is already 6 to 8 hours into phase I of the test at the beginning of the workday. Complete CDI and primary NDI must be ruled out before this modification to the modified water deprivation test is used; that is, the clinician must prove that the dog or cat requires at least 10 hours of water deprivation before 3% loss of body weight occurs. The modification described here should never be incorporated into the initial modified water deprivation test performed on the dog or cat.

Serial evaluation of body weight is a simple, inexpensive, reliable, and readily available method to determine the end point of phase I of the test. The goal is to lose 3% body weight during water deprivation. A 1% to 2% loss of weight due to dehydration may fail to maximally stimulate AVP secretion. False plateaus in urine osmolality and urine specific gravity have been observed with weight loss in the range of 2%, which can be misleading.

Other criteria have been used to determine whether and when maximal urinary concentration has been achieved through water deprivation. One method is recognition of a "plateau," or lack of increase, in urine osmolalities. This criterion is based on the knowledge that after the maximal renal response to water deprivation is achieved, the urine osmolality becomes relatively constant. This plateau in urine concentration is defined as a change in osmolality between three consecutive urine collection periods, 1 hour apart, of less than 5% or 30 mOsm/kg of H_2O. Monitoring urine specific gravity in lieu of osmolality or body weight is less reliable because false plateaus in urine specific gravity are common, even before 3% loss of body weight has occurred. Although the ability to ascertain a specific gravity is readily available, it is not sufficiently accurate to use as a criterion for ending phase I of the study, unless the urine specific gravity exceeds 1.030.

Monitoring skin turgidity and measuring the packed cell volume of blood have not proved to be reliable or consistent tools for recognizing dehydration. Measurement of total plasma protein concentration may be more reliable than the former two
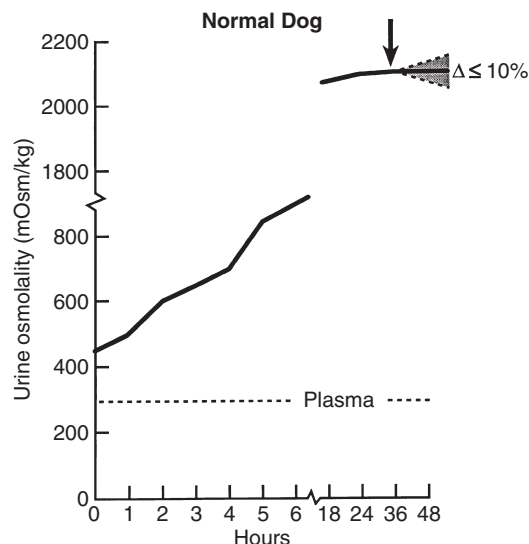

FIGURE 1-14 The effect of water deprivation on the urine osmolality of a normal dog. ↓ represents an injection of aqueous vasopressin, which alters urine osmolality 10% or less.

parameters, but monitoring cannot be considered as consistent or informative as body weight and patient observation. One important aid during phase I of the modified water deprivation test is the periodic check of the BUN and serum sodium concentration. Whenever the BUN rises above 30 mg/dL, the patient is azotemic and phase I should be ended; development of azotemia suggests occult renal disease. Azotemia developing during the modified water deprivation test has not resulted in problems in dogs and cats monitored as suggested earlier. Similarly, hypernatremia and increased plasma osmolality are potent stimulants of AVP secretion; when identified, these findings suggest that phase I of the water deprivation test be ended.

Response to Exogenous Arginine Vasopressin (Phase II)

Phase I determines the effects of dehydration on endogenous AVP secretion and AVP action on the renal tubules. Phase II determines what effect, if any, exogenous AVP has on renal tubular ability to concentrate urine in the face of dehydration. This phase differentiates impaired AVP secretion from impaired renal tubular responsiveness to AVP. Synthetic aqueous vasopressin (Pitressin) at a dosage of 0.2 to 0.4 U/kg up to a maximum of 5U, is administered with a intramuscular (IM) injection, urine samples are obtained, and the bladder is emptied 30, 60 and 120 minutes following the injection. Alternatively, DDAVP injection may be administered at a dose of 5 µg subcutaneously (SC) and urine samples obtained and the bladder emptied 2 and 4 hours following injection. Specific gravity and/or urine osmolality are determined on these urine samples and the dog or cat is offered small amounts of water over the next 2 hours. Ultimately, the animal is returned to free-choice water. The water is initially offered in small amounts to prevent overzealous intake, which could result in vomiting or water intoxication.

Responses to the Modified Water Deprivation Test

Normal Dogs

Normal dogs dehydrate quite slowly (Fig. 1-14). The secretion of AVP in the normal dog results in exquisite conservation

of fluid over long time periods. Random urine samples from normal dogs with free access to water reveal a specific gravity of 1.006 to greater than 1.040 and an osmolality of 160 to greater than 2500 mOsm/kg of H_2O (uOsm; van Vonderen et al, 1997b). In a report on laboratory dogs, the range of values was narrower and maximal urine concentration was achieved in 20 dogs after an average of approximately 40 hours of water deprivation (Hardy and Osborne, 1979). Maximal urine osmolality ranged from 1700 to 2700 uOsm and specific gravity from 1.050 to 1.075. Urine concentration indices (specific gravity and osmolality) did not plateau after reaching maximal values. Most dogs reached a peak in urine concentration, followed by slight fluctuations below that value for the remaining period of water deprivation. No difference in testing parameters occurred between males and females. Although not specifically evaluated, similar findings are expected in the cat.

In a clinical setting, normal for the modified water deprivation test is defined as a urine osmolality significantly greater than plasma osmolality. Normal dogs and cats have urine that is typically greater than 1100 uOsm and a urine specific gravity greater than 1.030 after dehydration. If urine osmolality and specific gravity exceed these values, pituitary AVP secretion and renal responsiveness to AVP are considered intact, and there is no need to evaluate renal responsiveness to exogenous AVP.

What happens if AVP is injected after maximal urine concentration is reached via water deprivation in normal dogs and cats? As expected, such animals are experiencing maximal endogenous AVP secretion, and no further urine concentration can occur. Therefore, exogenous AVP should have little effect on urine concentration in these animals. After dehydration, changes in urine concentration of 10% or less of preinjection levels are not considered significant. Such lack of change is typical in dogs and cats with normal AVP secretion rates and renal responsiveness to AVP (see Fig. 1-14).

Central Diabetes Insipidus

Dogs and cats with severe (complete) CDI cannot concentrate urine to levels greater than plasma osmolality (280 to 310 mOsm/kg [pOms]), even with severe dehydration. In fact, the parameters of urine concentration change little, if any, with continuing water deprivation (Fig. 1-15). CDI may be subdivided into severe or partial deficiencies of AVP. The modified water deprivation test has been used to help differentiate between mild and severe forms of CDI. As previously described, mild states of dehydration, resulting in a 1% to 2% loss in body weight, cause sustained release of AVP in the normal subject. After maximal urine concentration occurs in the normal animal, it does not increase more than an additional 10% with the injection of aqueous vasopressin. If the administration of AVP to a dehydrated dog or cat causes a significant increase in the concentration of the urine, endogenous AVP production and/or secretion must be insufficient. In dogs and cats with severe AVP deficiency, the urine osmolalities do not reach 300 mOsm/kg with dehydration; however, the increase in osmolality after administration of vasopressin ranges from 50% to 600% greater than the preinjection level (Figs. 1-16 and 1-17).

Dogs and cats with partial AVP deficiencies can increase their urine osmolality above 300 mOsm/kg after dehydration, but they also experience a further 10% to 50% or greater increase in urine osmolality following administration of vasopressin
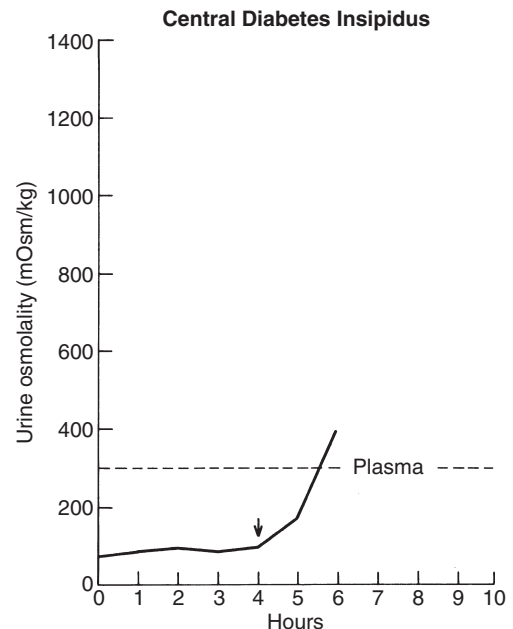

Central Diabetes Insipidus

FIGURE 1-15 The effect of water deprivation on the urine osmolality of a dog with severe central diabetes insipidus (CDI). ↓ represents an injection of aqueous vasopressin administered after 5% or more body weight is lost, causing greater than 50% increase in urine osmolality. Note how quickly these dogs lose 5% of their body weight.
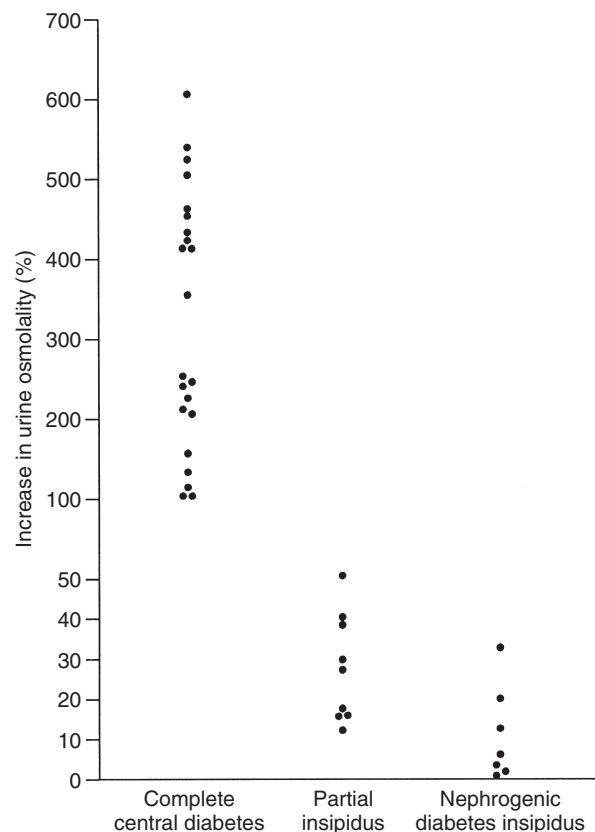

FIGURE 1-16 Increase in urine osmolality during phase III of the modified water deprivation test, that is, after intramuscular (IM) administration of aqueous vasopressin, in 22 dogs with complete central diabetes insipidus (CDI), 9 dogs with partial CDI, and 7 dogs with primary nephrogenic diabetes insipidus (NDI). Note the marked increase in urine osmolality after vasopressin administration with complete CDI versus partial CDI or primary NDI.
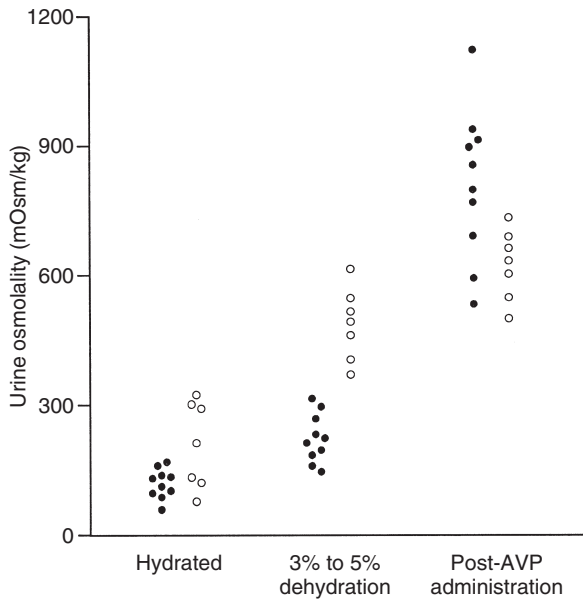
FIGURE 1-17 Urine osmolality in 10 dogs with complete central diabetes insipidus (CDI; *solid circle*) and 7 dogs with partial CDI *(open circle)* at the beginning (hydrated), end of phase II (3% to 5% dehydration), and end of phase III (post-arginine vasopressin [AVP] administration) of the modified water deprivation test. Note the relative failure of dogs with complete CDI to increase urine osmolality with dehydration and the marked increase in urine osmolality after aqueous vasopressin administration. The opposite occurred in the dogs with partial CDI.
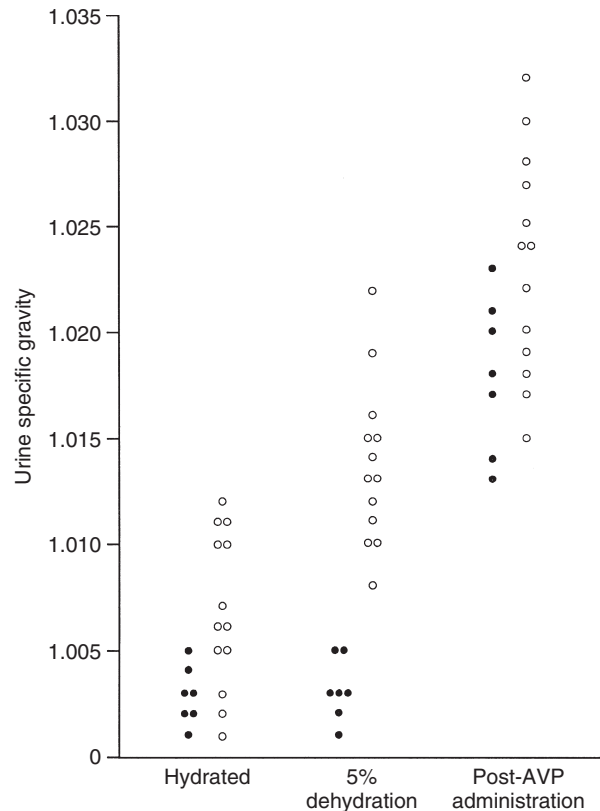

FIGURE 1-18 The effect of water deprivation on the urine osmolality of a dog afflicted with partial central diabetes insipidus (CDI) or canine hyperadrenocorticism. ↓ represents an injection of aqueous vasopressin administered after 5% or more body weight is lost owing to fluid loss via the urine. The urine osmolality did increase, but subnormally, in response to dehydration. Vasopressin results in a further 10% to 50% increase in urine osmolality. Note that the dog with partial CDI takes longer to dehydrate than one with severe CDI (see Fig. 1-15).

FIGURE 1-19 Urine specific gravity in 7 dogs with complete central diabetes insipidus (CDI; *solid circle*) and 13 dogs with partial CDI *(open circle)* at the beginning (hydrated), end of phase II (5% dehydration), and end of phase III (post-arginine vasopressin [AVP] administration) of the modified water deprivation test. Note the similarity of response between urine specific gravity and urine osmolality (see Fig. 1-17).
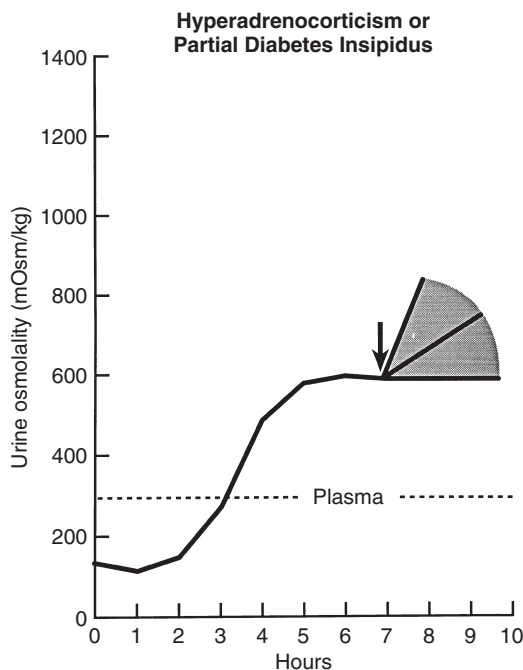
(Fig. 1-18; see Fig. 1-17). Changes in urine specific gravity often behave in a manner similar to changes in urine osmolality (Fig. 1-19; see Table 1-4). However, in some dogs and cats, urine specific gravity is not as easy to interpret as is urine osmolality (Fig. 1-20).

Primary Nephrogenic Diabetes Insipidus

Dogs, and presumably cats, afflicted with primary NDI cannot concentrate urine to levels greater than plasma osmolality (280 to 300 pOsm), even after severe dehydration. As with CDI, the parameters of urine concentration change little, if any, with continuing water deprivation (Fig. 1-21; see Table 1-4). Unlike CDI, however, minimal to no increase in urine osmolality and urine specific gravity occurs after administration of AVP (see Fig. 1-16).

Similar to dogs with severe CDI, dogs with primary NDI dehydrate quickly without water (see Table 1-4). The only difference between primary NDI and severe CDI is the lack of response to DDAVP seen in primary NDI versus the dramatic increase in urine concentration seen in CDI after DDAVP administration. Dogs with primary NDI are young and have a history of polyuria and polydipsia their entire life. In contrast, dogs and cats with acquired NDI are usually adults with a concurrent illness that interferes with AVP action at the renal tubular level and have a history of normal water intake and urination habits prior to the onset of polyuria and polydipsia. Acquired NDI patients are usually differentiated from those with CDI or primary NDI after review of the history, physical examination, and results of routine blood and

urine tests and diagnostic imaging, eliminating the need for the modified water deprivation test.

Psychogenic Polydipsia

Dogs, and presumably cats, with psychogenic polydipsia have an intact hypothalamic pituitary renal tubular axis for controlling fluid balance and variable severity of renal medullary solute washout. These dogs can concentrate urine to an osmolality above that of plasma with complete water deprivation and, given enough time, can attain urine specific gravities in excess of 1.030. Depending on the severity of renal medullary solute washout, it may take 24 hours or longer of water deprivation to attain concentrated urine. The previously described progressive water restriction procedure preceding the water deprivation test aids in reestablishing the renal medullary concentration gradient in these dogs and shortens the time to attain concentrated urine. Phase II (response to DDAVP administration) is rarely needed in dogs with psychogenic polydipsia. If phase II is performed, administration of DDAVP to a dehydrated dog with psychogenic polydipsia causes little change (< 10%) in urine osmolality (Fig. 1-22). This lack of change reflects the competent AVP secretory response of the posterior pituitary to dehydration and a response to AVP by the renal tubules.

Misdiagnosis (Inaccuracies) Using the Modified Water Deprivation Test

The modified water deprivation test is an excellent study to differentiate primary NDI from CDI, but it may not differentiate partial CDI from psychogenic polydipsia with complete certainty (Fig. 1-23). Difficulties in differentiating partial CDI from psychogenic polydipsia may be explained by two associated changes in the renal response to AVP. First is the reduction in maximal concentrating capacity resulting from chronic polyuria itself (i.e., renal medullary solute washout), which is manifested as subnormal urine concentrations in the presence of excess levels of plasma vasopressin. Second, there appears to be an enhanced antidiuretic response to low levels of plasma AVP in patients with CDI; that is, these patients have a supersensitive response to the small amount of AVP they secrete endogenously (Block et al, 1981).

TABLE 1-4   GUIDELINES FOR INTERPRETATION OF THE WATER DEPRIVATION TEST*

DISORDER	Urine Specific Gravity			Time to 5% Dehydration (Hours)	
	INITIALLY	5% DEHYDRATION	POST-ADH	MEAN	RANGE
CDI					
Complete	< 1.006	< 1.006	> 1.010	4	3-7
Partial	< 1.006	1.008–1.020	> 1.015	8	6-11
Primary NDI	< 1.006	< 1.006	< 1.006	5	3-9
Primary polydipsia	1.002-1.020	> 1.030	NA	13	8-20

ADH, Antidiuretic hormone; CDI, central diabetes insipidus; NA, not applicable; NDI, nephrogenic diabetes insipidus.
*Based on results from 20 dogs with CDI, 5 dogs with primary NDI, and 18 dogs with primary (psychogenic) polydipsia.
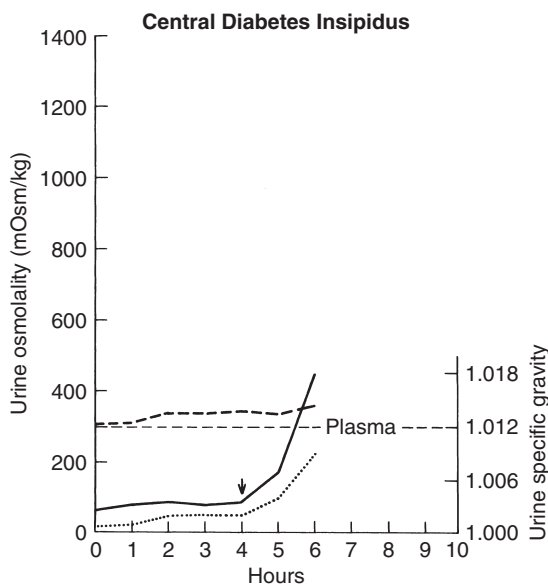

FIGURE 1-20 Same dog as in Figure 1-15. *Solid line,* Urine osmolality; *dashed line,* increasing plasma osmolality caused by dehydrating a dog with central diabetes insipidus (CDI); *dotted line,* urine specific gravity, illustrating why it is a less precise and less obvious diagnostic marker with severe CDI (see Fig. 1-15).
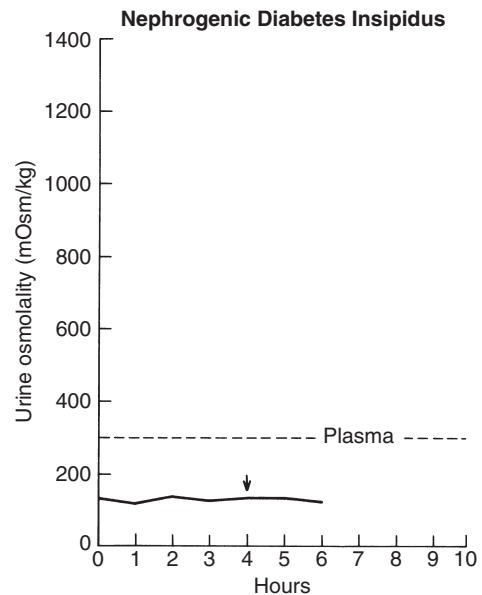

FIGURE 1-21 The effect of water deprivation on the urine osmolality of a dog afflicted with primary nephrogenic diabetes insipidus (NDI). Vasopressin is administered (↓) after 5% or more of body weight is lost (in this dog, after only 4 hours). Note the rapid loss of weight and the absence of any increase in urine concentration following 5% or more loss in body weight. The urine osmolality is not increased by vasopressin administration (< 10% change).

The consequence of the enhanced antidiuretic effect is the amelioration of the urinary manifestations of partial AVP deficiency. Therefore, patients with partial CDI and those with psychogenic polydipsia (that have not attained 3% loss of body weight) may respond to fluid deprivation with similar levels of urine concentration that cannot be increased further by injections of AVP (see Figs. 1-17 and 1-21). Thus neither the absolute level of urine osmolality achieved during fluid deprivation nor the percentage of increase evoked by exogenous AVP consistently permits a clear distinction between the two disorders (Zerbe and Robertson, 1981).

The modified water deprivation test may also occasionally misdiagnose human patients with congenital NDI. This inconsistency arises because a small perce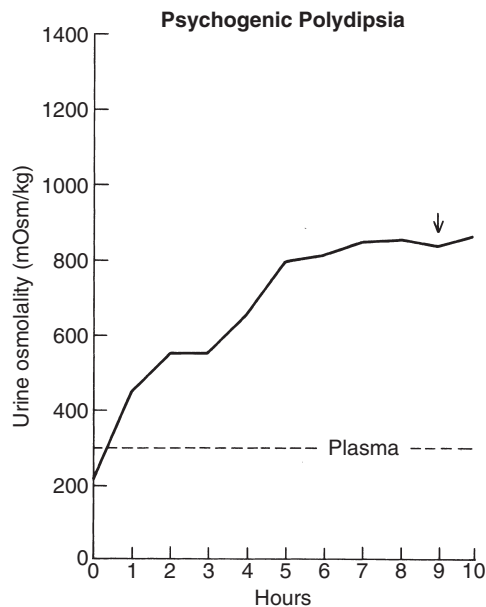ntage of these patients are only partially resistant to the antidiuretic effect of vasopressin and can concentrate their urine to some degree if the plasma levels of the hormone are quite high (Robertson and Scheidler, 1981). Because the standard diagnostic dose of aqueous AVP customarily produces marked hypervasopressinemia, patients with partial resistance may respond in this phase of the modified water deprivation test as though they had CDI (Zerbe and Robertson, 1981). Partial resistance to the antidiuretic actions of vasopressin has been documented in Huskies with primary NDI (Luzius et al, 1992), raising the possibility, albeit an uncommon one, that the modified water deprivation test could misdiagnose primary NDI in dogs too.

A number of humans have been incorrectly diagnosed as having primary (psychogenic) polydipsia. The diagnosis was initially based on results of a modified water deprivation test similar to that illustrated in Fig. 1-22. However, sophisticated studies have revealed that some individuals have a metabolic explanation for such a test result. These patients have an abnormal "osmostat" (i.e., an abnormally elevated set point in their osmoreceptors for stimulating release of AVP). Therefore, at a relatively high plasma osmolality, which should cause release of AVP, these individuals remain "AVP free," polyuric, and thus polydipsic. Similarly, such patients may have a lower than normal set point for thirst (i.e., thirst may be stimulated at a plasma osmolality of 290 pOsm when it should not be stimulated until the osmolality reaches 295 or 300 pOsm). A similar phenomenon has been described in four dogs with suspected primary polydipsia, in which the AVP response to hypertonic saline infusion was abnormal and suggested a primary disturbance in the regulation of AVP secretion (van Vonderen et al, 1999).

Approach If the Dog or Cat Is Brought into the Hospital Dehydrated

Occasionally, pets with severe polydipsia and polyuria appear clinically dehydrated or have developed hypernatremia before the modified water deprivation test can be undertaken. The most common cause for this dehydration is the owner's withholding of water in an attempt to reduce the likelihood of urination in the home. If the dehydrated dog or cat exhibits CNS signs, immediate fluid therapy should be initiated. However, if the pet is in no apparent distress, the bladder can be drained and the urine checked for specific gravity and osmolality. A serum sample can be obtained to assess BUN, sodium, osmolality, and vasopressin concentrations.
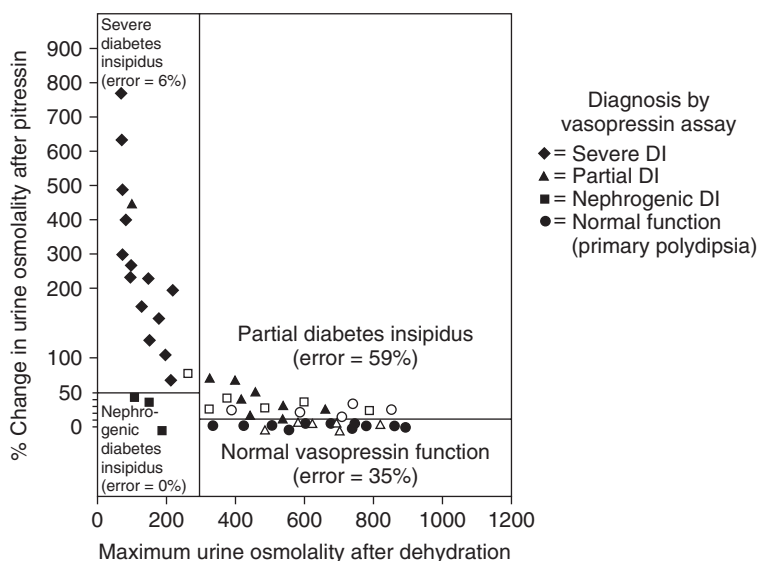

FIGURE 1-22 The effect of water deprivation on the urine osmolality of a dog afflicted with psychogenic polydipsia. Although these dogs are hormonally normal, the chronic diuresis may inhibit normal concentrating ability. ↓ represents an injection of aqueous vasopressin administered after 5% or more body weight is lost as a result of the unabated diuresis. The urine does show mild concentrating ability with dehydration, but less than 10% change in concentration following vasopressin administration.

FIGURE 1-23 Relationship between maximum urine osmolality after dehydration and percentage of increase in urine osmolality after vasopressin administration in humans with central diabetes insipidus (CDI) and nephrogenic diabetes insipidus (NDI) and primary polydipsia. Note the overlap in results between patients with partial CDI and patients with normal vasopressin function (i.e., primary polydipsia). (From Robertson GL: *The Endocrine Society 41st postgraduate annual assembly syllabus,* New Orleans, October, 1989, p. 25.)

BOX 1-3   Protocol for the Modified Water Deprivation Test

Preparation for the Test
A. Determine total water intake per 24 hours based on unrestricted access to water
B. Several days prior to the test, gradually decrease total 24 hour water intake by approximately 10% every 1 to 2 days; continue until the goal of 100 mL/kg/24 h is attained or the animal becomes aggressive for water
C. Withhold food beginning 12 hours before the test

Phase I: Water Deprivation
A. Prior to initiation
   1. Withdraw food and all water
   2. Empty bladder completely
   3. Obtain exact body weight
   4. Check urine specific gravity and, if available, osmolality
   5. Obtain serum osmolality
   6. Obtain BUN and serum electrolytes
   7. Check hydration and CNS status
B. During the test
   1. Empty bladder every 60 to 120 min
   2. Check exact body weight every 60 min
   3. Check urine specific gravity/osmolality at each interval
   4. Check hydration and CNS status at each interval
   5. Periodically recheck BUN and serum electrolytes

C. End of phase I
   1. If urine specific gravity exceeds 1.030
   2. When dog is clinically dehydrated or appears ill
   3. When dog has lost 3% body weight
      a. Obtain plasma for vasopressin concentration if available
      b. Empty bladder
      c. Check urine specific gravity/osmolality
      d. Check BUN and serum electrolytes
      e. Check serum osmolality

Phase II: Response to Exogenous AVP
A. Administer aqueous vasopressin 0.2 to 0.4 U/kg (max, 5U) IM or desmopressin acetate injection 5 μg SC
B. Continue withholding food and water
C. Monitor patient
   1. Empty bladder every 30 minutes for 2 hours maximum (aqueous vasopressin) or at 2 and 4 hours (desmopressin)
   2. Check urine specific gravity/osmolality
   3. Monitor hydration and CNS status

At End of Test
A. Introduce small amounts of water (10 to 20 mL/kg) every 30 minutes for 2 hours and monitor patient
B. If patient is well 2 hours after ending test, return to ad libitum water

AVP, Arginine vasopressin; *BUN*, blood urea nitrogen; *CNS*, central nervous system; *IM*, intramuscular; *SC*, subcutaneous.

The clinician can then proceed with the next phase of the modified water deprivation test (phase II; see Box 1-3) if the urine present in the bladder has a specific gravity of less than 1.030 (osmolality < 1100 uOsm) and the dog or cat is not uremic or hypernatremic. If the urine is more concentrated than 1.030 (1100 uOsm), a normal pituitary-renal tubular concentrating axis probably exists. If the animal is truly polyuric/polydipsic, psychogenic polydipsia and hyperadrenocorticism remain possible diagnoses. If the urine is dilute, response to exogenous vasopressin administration should help to establish the diagnosis.

Complications of the Modified Water Deprivation Test: Hypertonic Dehydration and Hypernatremia

An adult dog or cat is composed of 60% water. This water is subdivided into an intracellular compartment, which accounts for two-thirds of the total, and an extracellular compartment, which is one-third (Fig. 1-24). Movement of solutes that readily diffuse across all membranes (e.g., urea) is not accompanied by appreciable fluid shifts, because these solutes generate equal osmotic forces on either side of the cell membrane. Increased concentration of these solutes creates hyperosmolality in all fluid compartments because of a lack of water redistribution.

Solutes that are less permeable across cell membranes by virtue of molecular size, electrical charge, or active membrane pumps create an effective osmotic force. Intracellular solutes of this kind include potassium, phosphate, glucose and protein. Sodium and its anions serve the same purpose in the extracellular fluid (ECF). Increased concentrations of such solutes in the ECF produce hyperosmolality and hypertonicity. The osmotic gradient that is formed results in movement of intracellular fluid (ICF) into the extracellular space. Therefore, extracellular volume increases at the expense of cellular hydration. Alternatively, decreased concentrations of extracellular solutes produce a hyposmotic, hypotonic ECF that necessitates intracellular
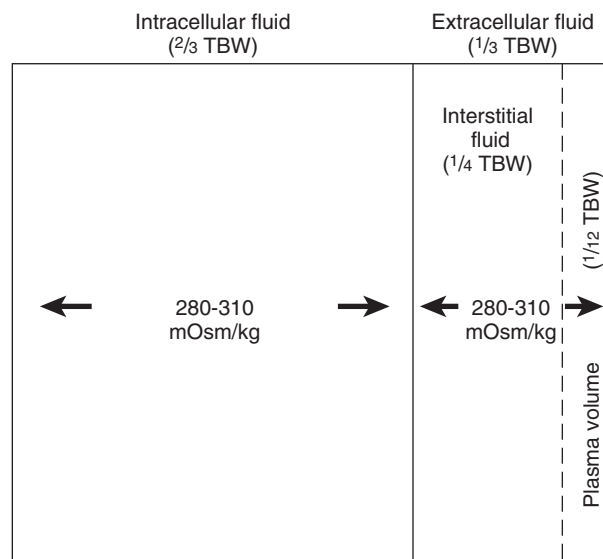

FIGURE 1-24 In the hydrated state, uniform total body water (TBW) distribution is maintained between the intracellular fluid (ICF) and extracellular fluid (ECF) compartments by osmotic forces (normal range, 280 to 310 mOsm/kg; average, 295 mOsm/kg) generated by solutes. (From Edwards DF, et al.: Hypernatremic, hypertonic dehydration in the dog with diabetes insipidus and gastric dilatation volvulus, *J Am Vet Med Assoc* 182[9]:973-977, 1983.)

movement of water, causing both hypovolemia and cellular overhydration (Edwards et al, 1983).

Three chemically distinct forms of dehydration (isotonic, hypotonic, and hypertonic) occur in veterinary practice. Isotonic dehydration is produced by proportional loss of water and electrolytes (solutes) (Fig. 1-25, *A*). Protracted vomiting and diarrhea are one cause of isotonic dehydration, in which water and electrolyte losses occur predominantly from the ECF compartment to the external
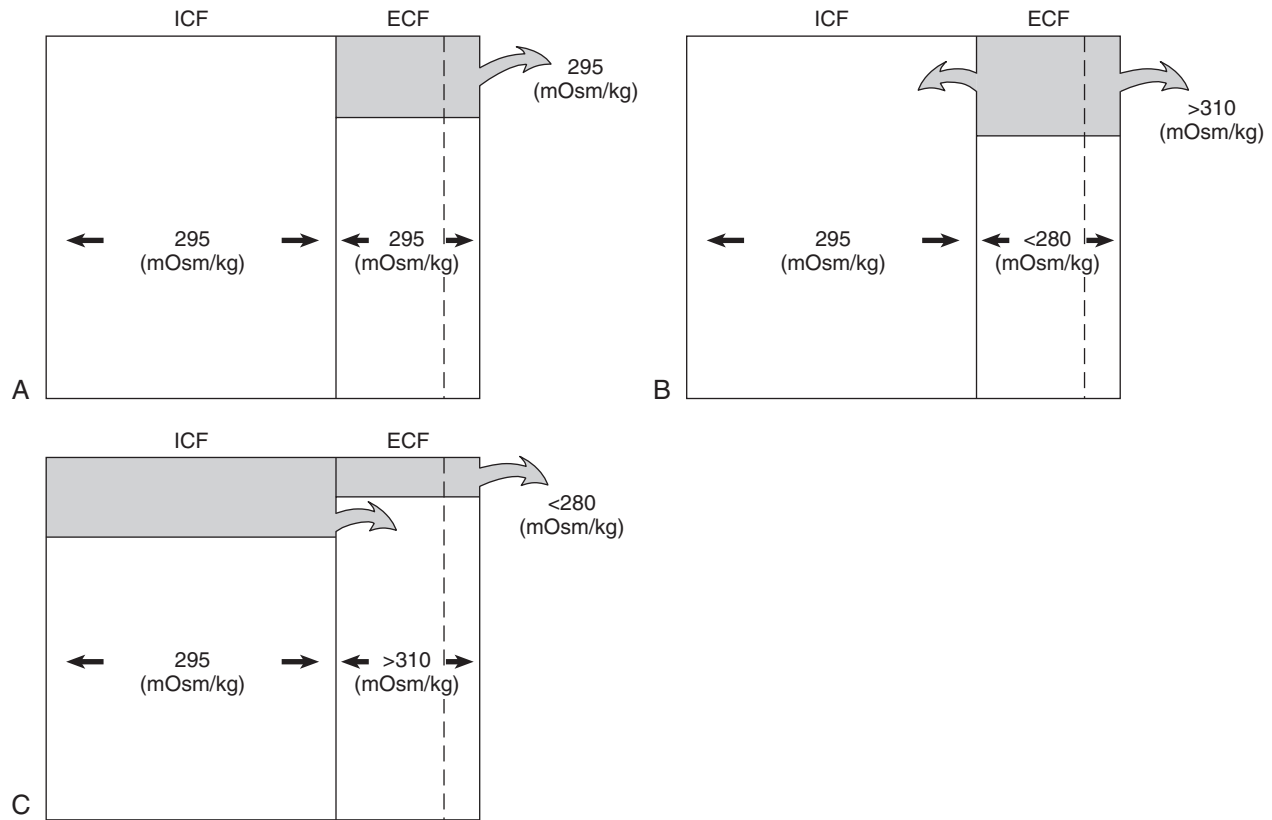
FIGURE 1-25 A, Isotonic dehydration results from extracellular fluid (ECF) loss of water and electrolytes isosmotic (295 mOsm/kg) to total body water (TBW). Because compartmental osmolality and tonicity remain unchanged (295 mOsm/kg), no major shift of intracellular fluid (ICF) occurs. **B,** Hypotonic dehydration results from ECF loss of water and electrolytes hyperosmotic (> 310 mOsm/kg) to TBW. The ECF becomes hypo-osmolar and hypotonic (< 280 mOsm/kg) to ICF. The intracellular movement of ECF reestablishes compartmental equilibrium at a lower osmotic pressure (<295 mOsm/kg) and minimizes fluid loss from the ICF space. **C,** Hypertonic dehydration results from ECF loss of water and electrolytes hyposmotic (< 280 mOsm/kg) to TBW. The ECF becomes hyperosmolar and hypertonic (> 310 mOsm/kg) and minimizes fluid loss from the ECF space. (From Edwards DF, et al.: Hypernatremic, hypertonic dehydration in the dog with diabetes insipidus and gastric dilatation volvulus, *J Am Vet Med Assoc* 182[9]:973-977, 1983.)

environment. Serum sodium concentrations are generally normal, and clinical signs (e.g., skin turgidity/elasticity) are proportional to the degree of hypovolemia.

Hypotonic dehydration is produced by loss of electrolytes in excess of water, as is seen in hypoadrenocorticism. In this example, excessive sodium is lost in the urine and gastrointestinal tract, creating a hypotonic extracellular compartment that loses water to both the external environment and the intracellular space. Serum sodium values are generally low in this condition, prerenal azotemia is common, and these animals exhibit more obvious signs of hypovolemia than those with isotonic dehydration (Fig. 1-25, *B*).

Hypertonic dehydration is produced by loss of water in excess of electrolytes and is the major concern after water deprivation in a dog or cat with CDI, primary NDI, or psychogenic polydipsia and in dogs and cats with inadequate fluid intake following the onset of trauma-induced CDI (Fig. 1-25, *C*). The hypertonic extracellular compartment preserves volume by dehydrating the intracellular compartment. The total water deficit is shared by fluid compartments in proportion to their normal content of water (Edwards et al, 1983). The cells, which contain two-thirds of the total body water, lose substantially more fluid than does the extracellular compartment. Plasma volume, constituting only one-twelfth of the total body water, is relatively well preserved under these circumstances. Thus hypertonic dehydration results in few of the expected signs of severe fluid depletion. Tachycardia,

lack of skin turgidity/elasticity, decreased pulse pressure, and decreased vascular volume are not detected until severe dehydration is present. Weight loss is consistently seen much sooner and further emphasizes the importance of monitoring body weight during a water deprivation test.

Severe hypernatremia with hyposthenuria are classic markers for hypertonic dehydration in the dog or cat with CDI or primary NDI. Other causes of hypernatremia are not typically associated with hyposthenuria (Box 1-4). The predominant clinical signs associated with hypertonic dehydration result from CNS dysfunction. The initial critical signs include irritability, weakness, and ataxia; as the hypernatremia worsens, stupor progresses to coma and seizures. The progression and severity of these signs depend on the rate of onset, degree, and duration of hypernatremia. Sodium has limited access to brain cells and is slow to equilibrate with the CSF. Rapidly developing severe hypernatremia results in a shift of water from the intracellular to the extracellular space and forces reduction in CSF volume as water crosses into the hyperosmotic fluid outside the CSF, causing shrinkage of the brain. Reduction in brain size leads to tearing of veins, subdural hemorrhage, and venous thrombosis. The brain synthesizes intracellular cerebral osmolar active substances (i.e., polyols) to compensate for the hyperosmolar ECF and to minimize the shift of fluid into the extracellular space. Osmolytes are produced in the brain beginning within 1 hour after induction of persistent hyperosmolality of ECF (Pollock and Arieff, 1980).

BOX 1-4   Causes of Hypernatremia in Dogs and Cats

Caused by Pure Water Loss
Central diabetes insipidus (CDI)*
Nephrogenic diabetes insipidus (NDI)*
Hypodipsia-adipsia
    Neurologic disease
    Abnormal thirst mechanism
    Defective osmoregulation of vasopressin release
Inadequate access to water
High environmental temperature (heat stroke)
Fever

Hypotonic Fluid Loss
Gastrointestinal fluid loss*
    Vomiting
    Diarrhea
Chronic renal failure*
Polyuric acute renal failure*
Osmotic diuresis
    Diabetes mellitus
    Mannitol infusion
Diuretic administration
Postobstructive diuresis
Cutaneous burns
Third-space loss
    Pancreatitis
    Peritonitis

Excess Sodium Retention
Primary hyperaldosteronism
Iatrogenic
    Salt poisoning
    Hypertonic saline infusion
    Sodium bicarbonate therapy
    Sodium phosphate enemas
    Parenteral nutrition*

Modified from DiBartola SP: Disorders of sodium and water: hypernatremia and hyponatremia. In DiBartola SP, editor: *Fluid, electrolyte and acid-base disorders in small animal practice*, ed 3, St Louis, 2006, Saunders/Elsevier.
*Common causes.

The goal in treating hypernatremic, hypertonic dehydration is to restore the ECF volume to normal and correct water deficits at a fluid rate that avoids significant complications. Because the brain adjusts to hypertonicity by increasing the intracellular solute content via the accumulation of idiogenic osmoles, the rapid repletion of body water with ECF dilution causes translocation of water into cells and can cause cerebral edema (Edwards et al, 1983; Reeves et al, 1998). If slower water repletion is undertaken brain cells lose the accumulated intracellular solutes and osmotic equilibration can occur without cell swelling.

The initial priority is to restore the ECF volume to normal. The choice of fluid to be administered depends on whether circulatory collapse is present, the rate at which hypernatremia developed, and the magnitude of the hypernatremia. In patients with modest volume contraction (e.g., tachycardia, dry mucous membranes, slow skin turgor), fluid deficits should be corrected with 0.9% saline supplemented with an appropriate amount of potassium. In replacing deficits, rapid administration of fluids is contraindicated unless there are signs of significant hypovolemia. Any fluid should be administered in a volume only large enough to correct hypovolemia. Serum sodium concentration should be measured frequently (every 4 to 6 hours) to assess response to treatment and status of the CNS evaluated frequently for change in clinical signs. Worsening neurologic status or sudden onset of seizures during fluid therapy is generally indicative of cerebral edema and the need for hypertonic saline solution or mannitol therapy.

Once ECF deficits have been replaced, the serum sodium concentration should be reevaluated and water deficits corrected if hypernatremia persists. An approximation of the free water deficit in liters may be calculated using the following formula:

$$(\text{current } [Na^+] \div \text{normal } [Na^+] - 1) \times (0.6 \times \text{body weight in kg})^2$$

Oral fluid administration is preferable for correcting water deficits, with fluid administered through an IV route if oral administration is not possible. Maintenance crystalloid solutions (e.g., half-strength [0.45%] saline solution with 2.5% dextrose or half-strength lactated Ringer's solution with 2.5% dextrose) should be used to correct the water deficit in hypernatremic animals with normal perfusion and hydration and should also be used in dehydrated animals with persistent hypernatremia after the correction of fluid deficits. Dextrose 5% in water (D5W) solution can be substituted for maintenance crystalloid solutions if the hypernatremia does not abate after 12 to 24 hours of fluid therapy.

The water deficit should be replaced slowly. Approximately 50% of the water deficit should be corrected in the first 24 hours, with the remainder corrected over the ensuing 24 to 48 hours. The serum sodium concentration should decline slowly, preferably at a rate of less than 1 mEq/L/hr. The rate of fluid administration should be adjusted as needed to ensure an appropriate decrease in the serum sodium concentration. A gradual reduction in the serum sodium concentration minimizes the fluid shift from the extracellular to the intracellular compartment, thereby minimizing neuronal cell swelling and cerebral edema and increasing intracranial pressure. A deterioration in CNS status after the start of fluid therapy indicates the presence of cerebral edema and the immediate need to reduce the rate of fluid administration. Frequent monitoring of serum electrolyte concentrations, with appropriate adjustments in the type of fluid administered and rate of fluid administration, is important in the successful management of hypernatremia. It is much simpler to avoid these complications by careful monitoring during water deprivation.

Plasma Vasopressin Determinations

The direct assay of plasma AVP substantially improves the accuracy of conventional tests used in the differential diagnosis of polyuria in humans (Zerbe and Robertson, 1981). The modified water deprivation test alone is consistently correct in establishing a diagnosis of severe CDI, because direct measure of AVP concentrations does not alter the results of tests in which a patient did not concentrate urine during dehydration. However, inaccuracies may occur in differentiating patients with partial CDI from those with primary polydipsia and primary NDI; incorporating plasma AVP determinations into the modified water deprivation test helps differentiate these disorders.

Reports incorporating plasma AVP measurements into the modified water deprivation test are sporadic in the veterinary literature. Plasma AVP concentrations failed to increase after 5% loss of body weight by water deprivation in two dogs with primary
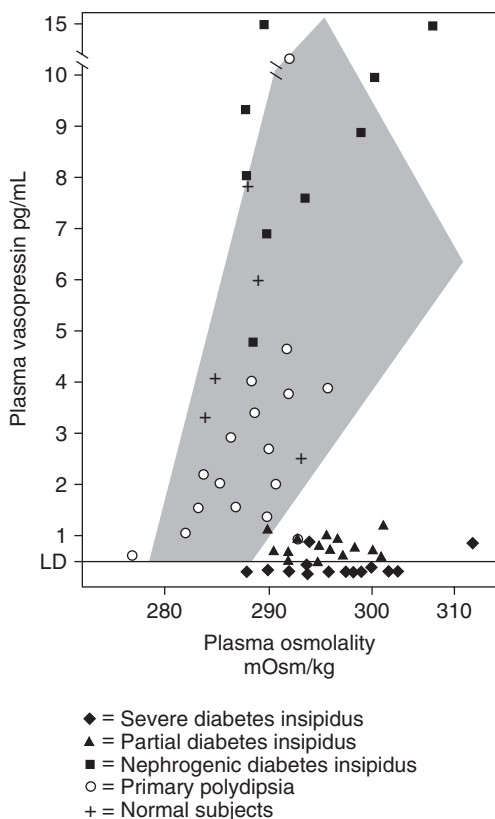
◆ = Severe diabetes insipidus
▲ = Partial diabetes insipidus
■ = Nephrogenic diabetes insipidus
○ = Primary polydipsia
+ = Normal subjects

FIGURE 1-26 Relationship of plasma arginine vasopressin (AVP) to plasma osmolality after dehydration in human beings with diabetes insipidus and primary polydipsia. Note that values from patients with central diabetes insipidus (CDI) fall below the normal range *(shaded area)*, whereas those from patients with nephrogenic diabetes insipidus (NDI) and primary polydipsia are almost always within or above the normal range. (From Robertson GL: Posterior pituitary. In Felig P, et al., editors: *Endocrinology and metabolism,* ed 2, New York, 1987, McGraw Hill, p. 338.) *LD,* Limit of detection.

◆ = Severe diabetes insipidus   ■ = Nephrogenic diabetes insipidus
▲ = Partial diabetes insipidus   ○ = Primary polydipsia
+ = Normal subjects

FIGURE 1-27 Relationship of urine osmolality to plasma vasopressin in human beings with diabetes insipidus and primary polydipsia. Note that values obtained during dehydration in humans with central diabetes insipidus (CDI) almost always fall within or above the normal range, whereas those from patients with nephrogenic diabetes insipidus (NDI) fall uniformly below normal. Values in most humans with primary polydipsia are normal, but a few may be subnormal, presumably as a consequence of washout of the medullary concentration gradient. (From Robertson GL: Posterior pituitary. In Felig P, et al., editors: *Endocrinology and metabolism,* ed 2, New York, 1987, McGraw Hill, p. 338.)

CDI compared with normal dogs (Post et al, 1989). Plasma AVP concentration was 3.3 and 3.7 pg/mL in these two dogs versus a mean of 31.3 pg/mL in three healthy dogs after water deprivation. A similar deficiency in plasma AVP after water deprivation was identified in a cat with CDI (plasma AVP, 1.3 pg/mL versus a mean of 84.6 pg/mL in eight healthy cats) (Brown et al, 1993). Plasma AVP concentrations remained within or below the reference range (i.e., less than 7 pg/mL) during water deprivation in four dogs with suspected primary polydipsia that were subsequently identified with a disturbance in the regulation of AVP secretion (van Vonderen et al, 1999).

When measurement of plasma AVP is incorporated into the modified water deprivation test, plasma for AVP determination should be obtained after 3% loss of body weight is caused by water deprivation but before exogenous AVP is administered (i.e., at the end of phase I). Plasma for AVP determination can also be obtained prior to water deprivation, although this may not be necessary. Commercially available canine and feline plasma AVP assays are not widely available in the United States, but this may change in the near future. Recently a commercially available human enzyme immunoassay kit for measurement of plasma AVP concentration was validated for use in dogs and the plasma concentration of AVP was significantly higher in dogs with congestive heart failure, compared with healthy dogs; results that suggest the assay may be diagnostically useful in dogs with suspected diabetes insipidus (Scollan et al, 2013).
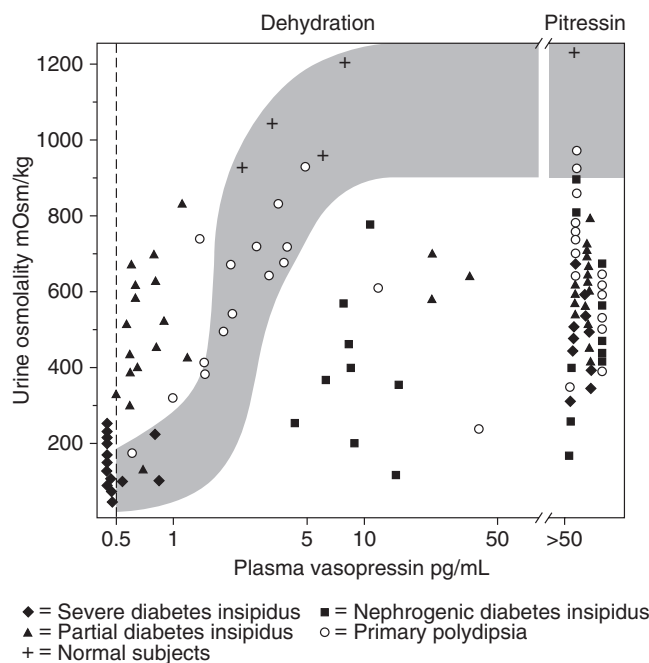
In humans, the plasma AVP value is interpreted in conjunction with the concurrent plasma and urine osmolality. When evaluating plasma AVP and plasma osmolality *concurrently* after dehydration, values from humans with severe or partial CDI fall below the normal range, whereas those from humans with NDI or primary polydipsia are almost always within or above the normal range (Fig. 1-26; Robertson, 1988). When plasma AVP and urine osmolality are evaluated *concurrently* after dehydration, values from humans with severe or partial CDI almost always fall within or above the normal range, whereas those from humans with NDI fall uniformly below normal (Fig. 1-27). In most cases, the values from humans with primary polydipsia are normal, but a few may be subnormal, presumably as a consequence of renal medullary solute washout. The AVP response to IV infusion of 20% saline was evaluated in conjunction with plasma and urine osmolality and results did not consistently distinguish between CDI, NDI, and primary polydipsia in 18 young dogs with polyuria and polydipsia suspected to have one of the these three disorders (van Vonderen et al, 2004). The authors speculated that the results of the study raise doubt about the generally accepted notion that AVP measurements during hypertonic saline infusion are the "gold standard" for the diagnostic interpretation of polyuria in dogs.

Until more extensive studies have been completed, we interpret plasma AVP concentrations after dehydration as follows: patients with severe or partial CDI should have AVP deficiencies, and those with primary NDI or primary/psychogenic polydipsia should have normal or excessive concentrations of AVP in the face of dehydration and subnormal urine osmolality (Table 1-5).

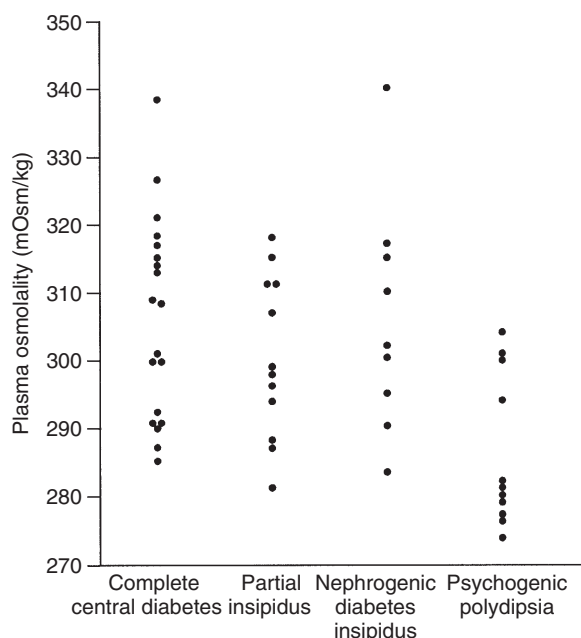| TABLE 1-5	RESULTS OF DIAGNOSTIC STUDIES IN DOGS WITH CENTRAL DIABETES INSIPIDUS, NEPHROGENIC DIABETES INSIPIDUS, AND PSYCHOGENIC POLYDIPSIA		
TEST	**CENTRAL DIABETES INSIPIDUS**	**NEPHROGENIC DIABETES INSIPIDUS**	**PSYCHOGENIC POLYDIPSIA**
Random plasma osmolality	Normal or ↑	Normal or ↑	Normal or ↓
Random urine osmolality	↓	↓	↓
Urine osmolality after water deprivation (≥ 3% loss of body weight)	No change	No change	↑
Urine osmolality during hypertonic saline infusion	No change	No change	↑
Urine osmolality after vasopressin administration	↑	No change	No change or mild ↑
Plasma vasopressin after water deprivation (≥ 3% loss of body weight)	Low	Normal or high	Normal or high

FIGURE 1-28 Random plasma osmolality in 19 dogs with complete central diabetes insipidus (CDI), 12 dogs with partial CDI, 9 dogs with primary nephrogenic diabetes insipidus (NDI), and 11 dogs with primary (psychogenic) polydipsia. Note the overlap in values between groups of dogs.

RANDOM PLASMA OSMOLALITY AS A DIAGNOSTIC TOOL

Measurement of random plasma osmolality may help identify primary or psychogenic polydipsia and should be done while the dog or cat has unrestricted access to water. Plasma osmolality in normal dogs and cats is approximately 280 to 300 pOsm. Dogs and cats with CDI and NDI have a primary polyuric disorder with secondary compensatory polydipsia; that is, they drink excessively because they urinate excessively. The stimulation for water intake in CDI and NDI is loss of free water through the kidneys, resulting in decreased blood volume and increased serum osmolality. Thus, patients with CDI and NDI should have high normal or high plasma osmolalities (Fig. 1-28). In contrast, dogs with primary or psychogenic polydipsia have a primary polydipsic disorder with secondary compensatory polyuria; that is, they urinate

excessively because they drink excessively. In these dogs, uncontrollable fluid intake raises blood volume and decreases plasma osmolality, which in turn causes decreased secretion of AVP and a decreased renal medullary concentration gradient, resulting in large urine volumes. Dogs with psychogenic polydipsia, in theory, should have plasma osmolalities on the low end of or below the reference interval.

It should be pointed out that the above discussion applies to the "classic" situation. Unfortunately, nature rarely provides us with "classic" patients. This is illustrated in a study of polyuric humans, in whom the serum osmolality varied from 281 to 298 sOsm in CDI, 285 to 292 in NDI, and 275 to 291 in primary polydipsia (Zerbe and Robertson, 1981). In our series of dogs, as well as those reported in the literature, plasma osmolality varied from 281 to 339 pOsm in CDI, 283 to 340 in NDI, and 274 to 304 in psychogenic polydipsia (see Fig. 1-28). Based on our experiences, a random plasma osmolality of less than 280 pOsm obtained while the dog or cat has free access to water suggests primary or psychogenic polydipsia, whereas a plasma osmolality greater than 280 pOsm is consistent with CDI, NDI, or psychogenic polydipsia.

ADDITIONAL DIAGNOSTIC TESTS: COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Neoplasia in the region of the pituitary and hypothalamus should be considered in the older dog or cat in which CDI develops. A complete neurologic evaluation, including CT or MRI may be warranted before idiopathic CDI is arbitrarily diagnosed, especially if the client is willing to consider radiation therapy or chemotherapy should a tumor be identified (see Fig. 1-9).

MRI has been used to identify the presence of vasopressin in the posterior pituitary in humans. On T1-weighted images, MRI produces a bright spot in the sella caused by stored hormone in the neurosecretory granules in the posterior pituitary (Moses et al, 1992; Kurokawa et al, 1998). The bright spot is present in approximately 80% of normal humans and is absent in patients with CDI, although some studies have identified a bright spot in patients with clinical evidence of CDI (Maghnie et al., 1997; Saeki et al., 2003). The bright spot decreases with a prolonged stimulus for vasopressin secretion and has been variably reported in other polyuric disorders (Fujisawa et al, 2004). A bright spot in the region of the posterior pituitary has also been identified in dogs and presumably represents vasopressin stored in neurosecretory
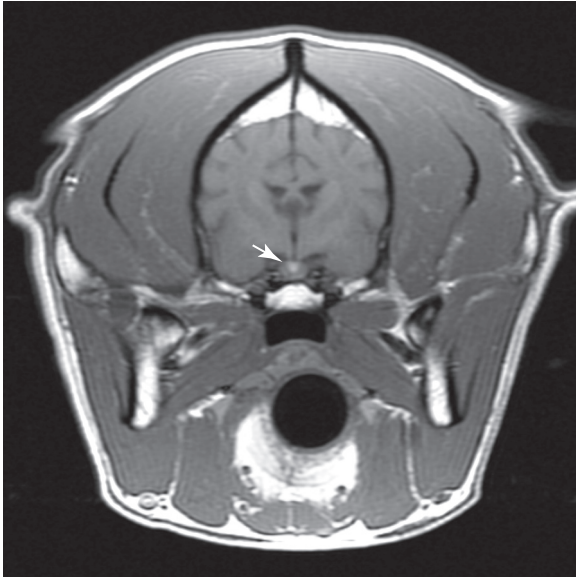
FIGURE 1-29 Magnetic resonance imaging (MRI) T1-weighted transverse image of the pituitary gland in a healthy adult dog illustrating the hyperintense "bright spot" *(arrow)* in the sella. In humans, the bright spot is caused by stored arginine vasopressin (AVP) in the neurosecretory granules in the posterior pituitary. Presumably the same is true in dogs.

granules (Fig. 1-29). Studies evaluating changes in the presence and intensity of the bright spot in dogs with polyuric disorders have not yet been reported.

TREATMENT

Therapeutic options for dogs and cats with diabetes insipidus are listed in Box 1-5.

Vasopressin Analogues (Used in Central Diabetes Insipidus and Partial Central Diabetes Insipidus)

The synthetic analogue of vasopressin, DDAVP (see Fig. 1-1), is the standard therapy for CDI. DDAVP has almost three times the antidiuretic action of AVP with minimal-to-no vasopressor or oxytocic activity (Robinson, 1976). Several extrarenal actions of DDAVP have also been described: release of two coagulation factors (Factor VIIIc and von Willebrand factor (Richardson and Robinson, 1985); a decrease in blood pressure and peripheral resistance; and an increase in plasma renin activity (Schwartz et al, 1985).

The metabolism of DDAVP in humans follows a bi-exponential curve with first and second half-lives of 7.8 and 75.5 minutes, respectively. Similar findings are noted in experiments with normal dogs (Ferring, 1985) and in spontaneous canine cases of CDI. Additionally, blood chemistry studies and necropsies on treated dogs (Ferring, 1985) and clinical experience in dogs and cats with CDI (Kraus, 1987; Harb et al, 1996; Oliveira et al, 2013) indicate that the drug is safe for use in dogs and cats.

The intranasal DDAVP preparation (DDAVP nasal, 2.5- and 5.0-mL bottles containing 100 µg DDAVP/mL) is used most commonly for treating CDI in humans and is effective for the treatment of CDI in dogs and cats (Harb et al, 1996). Administration of DDAVP nasal to dogs and cats via the intranasal route is possible but not recommended. DDAVP nasal should be

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BOX 1-5   Therapies Available for Polydipsic/Polyuric Dogs with Central Diabetes Insipidus, Nephrogenic Diabetes Insipidus, or Primary (Psychogenic) Polydipsia

A. CDI (severe)
  1. DDAVP
      a. Effective
      b. Expensive
      c. Oral tablets or drops of nasal solution in conjunctival sac
      d. DDAVP injection SC once or twice a day
  2. LVP (lypressin [Diapid])
      a. Short duration of action; less potent than DDAVP
      b. Expensive
      c. Requires drops into nose or conjunctival sac
  3. No treatment—provide continuous source of water
B. CDI (partial)
  1. DDAVP
  2. LVP
  3. Chlorpropamide
      a. 30% to 70% effective
      b. Inexpensive
      c. Pill form
      d. Takes 1 to 2 weeks to obtain effect of drug
      e. May cause hypoglycemia
  4. Thiazide diuretics
      a. Mildly effective
      b. Inexpensive
      c. Pill form
      d. Should be used with low-sodium diet
  5. Low-sodium diet
  6. No treatment—provide continuous source of water
C. NDI
  1. Thiazide diuretics—as described earlier
  2. Low sodium diet
  3. No treatment—provide continuous source of water
D. Primary (psychogenic) polydipsia
  1. Water restriction at times
  2. Water limitation
  3. Behavior modification
      a. Change environment
      b. Change in daily routine
      c. Increase daily exercise
      d. Increase contact with humans or dogs

CDI, Central diabetes insipidus; *DDAVP,* desmopressin acetate; *LVP,* lysine vasopressin; *NDI,* nephrogenic diabetes insipidus; *SC,* subcutaneous.

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transferred to a sterile eye dropper bottle and drops placed into the conjunctival sac of the dog or cat. Although the solution is acidic, ocular irritation rarely occurs. One drop of DDAVP nasal contains 1.5 to 4 µg of DDAVP, and a dosage of one to two drops administered once or twice daily controls signs of CDI in most dogs and cats.

Because of the expense of DDAVP nasal and loss of DDAVP drops from the conjunctival sac with head shaking, blinking, and inadvertent application of excessive amounts, our preference is to initially use DDAVP tablets (0.1 and 0.2 mg) when using response to DDAVP to establish the diagnosis of CDI and for long-term treatment of CDI. Clinical response in humans is variable, in part, because the bioavailability of DDAVP tablets is approximately 5% to 15% of the intranasal dose in humans. Similar information is

not available for dogs and cats. Our initial dose for DDAVP tablets is 0.05 mg for dogs weighing less than 5 kg and for cats, 0.1 mg for dogs weighing 5 to 20 kg, and 0.2 mg for dogs weighing more than 20 kg given every 12 hours. The frequency of administration is increased to every 8 hours if unacceptable polyuria and polydipsia persist 1 week after therapy is initiated. Treatment should be switched to DDAVP nasal if there is minimal to no response to oral DDAVP administered three times a day. Decreasing the frequency of administration of the tablets, decreasing the dose of DDAVP, or both can be tried once clinical response has been documented. To date, most dogs and cats have required 0.1 to 0.2 mg and 0.025 to 0.05 mg, respectively, of oral DDAVP two to three times a day to control polyuria and polydipsia (Aroch et al, 2005).

DDAVP parenteral (2 mL vials containing 4 μg/mL) can be used in lieu of the nasal formulation or oral tablets. In humans, parenteral administration of DDAVP is 5 to 20 times as potent as DDAVP nasal (Richardson and Robinson, 1985). The initial parenteral dosage of DDAVP is 0.5 to 1.0 μg administered SC once a day. Subsequent adjustments in the dose and frequency of administration are based on improvement in polyuria and polydipsia, duration of clinical response, and changes in serum sodium concentration. Hyponatremia is more apt to develop with parenteral DDAVP than with tablets or nasal spray and can mimic the syndrome of inappropriate vasopressin secretion.

In humans with CDI, a decrease in urine volume usually occurs within 2 hours after administration of DDAVP, regardless of the route of administration, and the total duration of action varies from 6 to 18 hours (Lam et al, 1996). Larger doses of DDAVP appear both to increase its antidiuretic effects and to prolong its duration of action; however, expense becomes a limiting factor. The medication may be administered exclusively in the evening as insurance against nocturia.

We have had excellent results in dogs and cats receiving daily medication for longer than 5 years. Owners of dogs and cats with CDI have reported that their pets become accustomed to receiving eye drops, mentioning eye or conjunctival irritation as an infrequent complication. If polyuria and polydipsia recur despite DDAVP therapy, several possibilities should be considered, including problems with owner compliance or administration technique, inadequate dose, outdated or inactivated DDAVP, or development of a concurrent disorder causing polyuria and polydipsia. Hyperadrenocorticism is the primary differential diagnosis when polyuria and polydipsia recur despite DDAVP treatment in a dog with CDI.

DDAVP was effective in Husky puppies with familial NDI caused by a defect in V_2 receptor binding affinity for AVP (Luzius et al, 1992). However, extremely high dosages (0.33 U/kg body weight intramuscularly three times a day) of DDAVP were required to obtain improvement in polyuria and polydipsia, dosages that most owners would consider cost-prohibitive. For practical purposes, DDAVP is considered ineffective in the treatment of NDI.

Oral Agents (Used in Central Diabetes Insipidus, Partial Central Diabetes Insipidus, Nephrogenic Diabetes Insipidus, and Primary Polydipsia)

Chlorpropamide

Chlorpropamide (Diabinese) is an oral sulfonylurea drug used for the treatment of hyperglycemia in humans. Largely by chance, chlorpropamide has also been found to be efficacious in treating humans with CDI and has been found to reduce urine output 30% to 70% in humans afflicted with partial CDI. This reduction

is associated with a proportional rise in urine osmolality, correction of dehydration, and a reduction in fluid consumption similar to that observed with small doses of vasopressin (Robertson, 1981).

The exact mechanism of the potentiating effect of chlorpropamide on the action of AVP in the kidney is not known. Chlorpropamide may enhance AVP stimulation of renal medullary cAMP by augmenting adenylate cyclase sensitivity to AVP or by inhibiting phosphodiesterase (Reeves et al, 1998). Inhibition of prostaglandin E_2 (PGE_2) synthesis, thereby removing an antagonist of AVP, has also been proposed as a mechanism for chlorpropamide potentiation. Finally, chlorpropamide treatment may augment AVP dependent NaCl absorption by the medullary thick ascending loop of Henle, thereby increasing the driving force for water absorption in collecting ducts (Kusano et al, 1983). Like DDAVP, chlorpropamide is ineffective in treating patients with NDI. Other drugs of the sulfonylurea class do not have a significant antidiuretic effect in CDI and, in some humans, may actually be mildly diuretic.

The effectiveness of chlorpropamide in the treatment of canine CDI is a matter unresolved in the literature. As in humans, use of the drug in dogs requires the presence of some endogenous AVP. Some veterinarians have had little or no success using chlorpropamide, citing a reduction in urine volume of only 18% during 7 days of therapy (Schwartz Porsche, 1980). Other veterinarians have claimed a 50% reduction in urine volume after 5 days of therapy. The drug has also had mixed results when used in cats with CDI (Kraus, 1987).

An effective dosage of chlorpropamide for the treatment of partial CDI has not been determined in the dog or cat, although 10 to 40 mg/kg/day has been suggested (Hardy, 1982). The dose of chlorpropamide used in the unsuccessful study in dogs was 250 mg twice daily (Schwartz Porsche, 1980) and was approximately 30 mg/kg/day in one cat that failed to respond (Kraus, 1987). The dosage was not mentioned in the dog study and was approximately 10 mg/kg/day in one cat in which chlorpropamide improved polyuria and polydipsia.

The primary adverse effect of chlorpropamide is hypoglycemia caused by chlorpropamide-induced insulin secretion. Regular feeding schedules should be adhered to if hypoglycemic problems are to be avoided. We have had little experience with chlorpropamide simply because our success with DDAVP has been excellent, and our owners have accepted the cost and difficulties encountered in treating their pets with this drug. If successful in a trial administration period, chlorpropamide may prove to be a valid alternative in treating partial CDI.

Thiazide Diuretics

The thiazide diuretics may reduce the polyuria in animals with diabetes insipidus (Breitschwerdt et al, 1981). This seemingly paradoxic effect is seen in NDI, as well as in CDI, suggesting that this therapeutic agent has a mode of action distinct from that of chlorpropamide. By inhibiting sodium reabsorption in the ascending limb of the loop of Henle, the thiazides reduce total body sodium concentrations, thus contracting the ECF volume and increasing salt and water resorption in the proximal renal tubule. This results in lower sodium concentrations in the distal renal tubule and less osmotic effect to maintain tubular volume, resulting in a reduction in urine volume. The net effect in diabetes insipidus is to cause a slight rise in urine osmolality and a proportionate reduction in urine volume. Depending on sodium intake, polyuria can be reduced 30% to 50% in humans with NDI or CDI. Apart from occasional hypokalemia, significant side effects are uncommon. The thiazides reduce the ability to excrete a water load and,

if given to a patient with primary polydipsia, may precipitate water intoxication (Robertson, 1981).

Chlorothiazides are recommended at a dose of 20 to 40 mg/kg twice daily, in concert with low-sodium diets. Periodic serum electrolyte determinations (every 2 to 3 months) should aid in avoiding iatrogenic problems.

Sodium Chloride (Salt) Restriction

Restricting salt intake, as the sole therapy in diabetes insipidus, reduces urine output by increasing the volume of filtrate absorbed isosmotically in the proximal nephron. This simple therapy may be helpful in the treatment of both CDI and NDI. Salt content of commercial dog and cat foods is quite variable, ranging from 0.14 to 3.27 g Na/Mcal for dog foods and 0.3 to 4.0 g Na/Mcal for cat foods. In general, diets considered lower in sodium content contain less than 1.0 g Na/Mcal.

No Treatment

Therapy for diabetes insipidus (CDI and NDI) and primary polydipsia is not mandatory as long as the dog or cat has unlimited access to water and is maintained in an environment where polyuria does not create problems. In most instances, untreated pets are outdoor animals. Some of our owners have elected not to treat their pets after the diagnosis is established. More commonly, owners have discontinued DDAVP treatment after 1 or 2 months of therapy, primarily because of the expense. Still others treat their pet with DDAVP periodically, when it is undesirable for the dog or cat to be exhibiting severe polyuria and polydipsia (e.g., relatives staying at the house). If an owner elects not to treat his or her pet, it is imperative that the dog or cat have access to a constant water supply because relatively short periods of water restriction can have catastrophic results, such as the development of hypernatremic, hypertonic dehydration, and neurologic signs; a complication that would occur with CDI and primary NDI but not psychogenic polydipsia.

Behavior Modification (Used in Psychogenic Polydipsia)

Water Restriction

Gradually limiting water intake to amounts in the high normal range (60 to 80 mL/kg/24 h) improves and may resolve polyuria and polydipsia in dogs with psychogenic polydipsia. In some dogs, rapid water restriction results in bizarre behavior, excessive barking, urine consumption, and dehydration. Therefore, we prefer to have the owner first calculate the dog's approximate water intake per 24 hours while free-choice water is allowed. This volume of water is then reduced by 10% per week until water volumes of 60 to 80 mL/kg/24 h are reached. The total 24-hour volume of water should be divided into several aliquots, with the last aliquot given at bedtime. Oral salt (1 g/30 kg twice a day) and/or oral sodium bicarbonate (0.6 g/30 kg twice a day) may also be administered for 3 to 5 days, to reestablish the medullary concentration gradient. We have had excellent success with gradual water restriction and do not routinely use oral salt or sodium bicarbonate.

Change in Environment

Changes in the dog's environment or daily routine should also be considered for dogs with psychogenic polydipsia, such as initiating a daily exercise routine, bringing a second pet into the home, providing some distraction (e.g., a radio playing when the clients are not home), or moving the dog to an area with an increased amount of contact with humans.

PROGNOSIS

Dogs and cats with idiopathic or congenital CDI usually become asymptomatic with appropriate therapy, and with proper care these animals have an excellent life expectancy. Unfortunately, many owners discontinue DDAVP therapy or elect euthanasia of their pet after a few months because of the expense of DDAVP. Without therapy, these animals often lead acceptable lives as long as water is constantly provided and they are housed in an environment that cannot be damaged by severe polyuria. However, the untreated animal is always at risk for developing life-threatening dehydration if water is withdrawn for longer than a few hours. Additionally, even mild illness that causes vomiting or reduces water intake can develop into one associated with severe dehydration. Thus, untreated dogs and cats carry a guarded prognosis.

In one study, long-term follow-up of 19 dogs with CDI found 7 of 19 dogs still alive a mean of 29 months (median, 30 months) from the time of diagnosis of CDI (Harb et al, 1996). Six of these seven dogs were 3 years of age or younger at the time CDI was diagnosed. Of the original 19 dogs, 12 had died within an average of 6 months (median, 2 months) after diagnosis of CDI. Three dogs died from unrelated or unknown causes, two dogs were euthanized shortly after the diagnosis of CDI was established, and seven dogs died or were euthanized because of development of neurologic disease. In these later seven dogs, neurologic signs developed 2 months (median, 1 month; range, 0.5 to 5 months) and the dogs were dead 3.3 months (median, 1.5 months; range, 1 to 7 months) after CDI was diagnosed (Harb et al, 1996). A mass in the region of the pituitary gland was identified by CT scan or at necropsy in six of the dogs in which these procedures were performed. The seven dogs that developed neurologic signs were older than 6 years of age.

Obviously, dogs with aggressive hypothalamic or pituitary problems, such as a growing tumor, have a grave prognosis. Treatment of tumors in the region of the hypothalamus and pituitary, using either irradiation (see Chapter 10) or chemotherapy (e.g., bis-chloroethylnitrosourea [BCNU]), can be tried; however, results are unpredictable. Polyuria and polydipsia typically persists despite radiation therapy, in part, because clinical signs of CDI do not develop until 90% of the magnocellular neurons are destroyed (Robinson and Verbalis, 2011). Based on experience with pituitary macrotumors, successful response to radiation therapy is more likely when the tumor is small and before neurologic clinical signs develop. CT or MRI scan is warranted at the time of diagnosis of CDI, especially when CDI is acquired in an older dog or cat.

The prognosis for dogs and cats with primary NDI is guarded to poor because of limited therapeutic options, the generally poor response to therapy, and the risk for developing severe dehydration and hypernatremia. The prognosis with acquired NDI depends on the prognosis of the primary problem.

The prognosis in psychogenic polydipsia is usually excellent. Water restriction and some form of behavior modification help most of these animals to become asymptomatic, although relapses do occur.

SYNDROME OF INAPPROPRIATE VASOPRESSIN SECRETION: EXCESS VASOPRESSIN

A primary excess of AVP occurs in two clinical settings—in the syndrome of inappropriate antidiuretic hormone (SIADH) and as a consequence of drugs that stimulate AVP secretion, activate renal V_2 receptors, or potentiate the antidiuretic effect of AVP (Box 1-6). In SIADH, sustained release of AVP occurs in

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BOX 1-6   Drugs and Hormones Reported to Affect Vasopressin Secretion or Action

Secretion

Stimulate AVP release	Inhibit AVP release
Acetylcholine	α-Adrenergic drugs
Anesthetic agents	ANP
Angiotensin II	Glucocorticoids
Apomorphine	Haloperidol
β-Adrenergic drugs	Oxilorphan
Barbiturates	Phenytoin
Carbamazepine	Promethazine
Clofibrate	
Cyclophosphamide	
Histamine	
Insulin	
Metoclopramide	
Morphine and narcotic analogues	
PGE$_2$	
Vincristine	

Renal

Potentiate AVP action	Inhibit AVP action
Aspirin	α-Adrenergic drugs
Carbamazepine	ANP
Chlorpropamide	Barbiturates
Nonsteroidal anti-inflammatory agents	Demeclocycline
Thiazides	Glucocorticoids
	Hypercalcemia
	Hypokalemia
	Methoxyflurane
	PGE$_2$
	Protein kinase C
	Tetracyclines
	Vinca alkaloids

ANP, Atrial natriuretic peptide; *AVP,* arginine vasopressin; *PGE$_2$,* prostaglandin E$_2$.

BOX 1-7   Conditions Associated with Syndrome of Inappropriate Antidiuretic Hormone in Humans

Malignant Neoplasia
Carcinoma; bronchogenic, pancreatic, prostatic, bladder
Lymphoma and leukemia
Thymoma and mesothelioma

Drug-Induced
ACE inhibitors
Chlorpropamide
Clofibrate
Clozapine
Cyclophosphamide
Omeprazole
Serotonin reuptake inhibitors
Thiazides
Vincristine
Others

Central Nervous System Disorders
Degenerative/demyelinating diseases
Head trauma
Infection
Inflammatory diseases
Porphyria
Tumors

Endocrine Diseases
Adrenal insufficiency
Pituitary insufficiency
Hypothyroidism

Pulmonary Disorders
Acute respiratory failure
Aspergillosis
Bacterial and viral pneumonia
Tuberculosis

Adapted from Ramsay DJ: Posterior pituitary gland. In Greenspan FS, Fosham PH, editors: *Basic and clinical endocrinology,* Los Altos, CA, 1983, Lange Medical Publications, p. 120.

ACE, Angiotensin converting enzyme.

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the absence of either osmotic or nonosmotic stimuli. In humans, SIADH has been observed in a variety of disorders, particularly pulmonary, CNS, and neoplastic disorders (Box 1-7) (Robinson and Verbalis, 2011). The most common association of SIADH is with tumors, most notably bronchogenic carcinomas. Vasopressin or a peptide having comparable biologic activity is produced by tumors. SIADH is rare in the dog and cat and has been reported in one dog with heartworm disease, one dog with liver disease, one dog with an undifferentiated carcinoma, one dog with a tumor in the region of the hypothalamus, one cat following anesthesia, laparoscopy and metoclopramide treatment, and was considered idiopathic in two dogs (Rijnberk et al, 1988; Houston et al, 1989; Cameron and Gallagher, 2010; Kang and Park, 2012).

As a result of sustained release of AVP or AVP-like peptides, patients retain ingested water and become hyponatremic and modestly volume-expanded and generally gain body weight (Robinson and Verbalis, 2011). This volume expansion results in reduced rates of proximal tubular sodium absorption and, consequently, natriuresis. Increased levels of ANP also contribute to the natriuresis. The diagnostic features that characterize this syndrome include hyponatremia, clinical euvolemia as defined by the absence of signs of hypovolemia (e.g., decreased skin turgor, tachycardia) and hypervolemia (e.g., subcutaneous edema, ascites), plasma hyposmolality (< 275 pOsm), urine osmolality greater than that appropriate for the concomitant osmolality of plasma, and increased renal sodium excretion despite hyponatremia. A similar clinical picture can be produced experimentally by giving high doses of AVP to a normal subject who receives a normal to increased fluid intake, with subcutaneous administration of high doses of parenteral DDAVP to dogs with CDI, and theoretically with administration of DDAVP to dogs with psychogenic polydipsia. Water restriction results in the plasma osmolality and serum sodium concentrations returning to normal (Aron et al, 2001; Cameron and Gallagher, 2010).

Four patterns of plasma AVP secretion have been described in humans with SIADH, suggesting four patterns of osmoregulatory defects in this syndrome. The most common derangement is random hypersecretion of AVP independent of osmotic and nonosmotic control (Robinson and Verbalis, 2011). This erratic and irregular secretion of AVP can be associated with both malignant and nonmalignant disease. Others include a "reset osmostat" system in which the threshold for AVP secretion is abnormally low but there is an appropriate response to changes in osmolality,

an "AVP leak" pattern characterized by inappropriate nonsuppressible basal AVP secretion but normal secretion in response to osmolar changes above plasma osmolality, and low to undetectable AVP concentrations despite classic clinical characteristics of SIADH. The pattern of SIADH that occurs without measureable AVP secretion may represent increased renal sensitivity to low circulating AVP concentrations, which is possibly a result of an activating mutation of the V_2 receptor (Kamoi, 1997; Feldman et al, 2005). Thus far, it has not been possible to correlate the pattern of AVP abnormality with the pathology of the syndrome. The threshold and sensitivity of vasopressin secretion were studied by infusion of hypertonic saline in two dogs with idiopathic SIADH (Rijnberk et al, 1988). One dog demonstrated a pattern of reset osmostat and the other, a pattern consistent with vasopressin leak.

Clinical signs of hyponatremia include lethargy, anorexia, vomiting, weakness, muscle fasciculations, obtundation, disorientation, seizures, and coma. CNS signs are the most worrisome, occur when hyponatremia is severe (< 120 mEq/L), and develop as changes in plasma osmolality cause fluid to shift from the extracellular to the intracellular space, resulting in neuronal swelling and lysis. The onset and severity of clinical signs depend on the rapidity with which the hyponatremia develops as well as on the degree of hyponatremia. The more chronic the hyponatremia and the more slowly it develops, the more capable the brain is of compensating for changes in osmolality through the loss of potassium and organic osmolytes from cells. Clinical signs develop when the decrease in plasma osmolality occurs faster than the brain's defense mechanisms can counter the influx of water into neurons.

The diagnosis of SIADH is made by excluding other causes of hyponatremia (see Chapter 12) and meeting the following criteria: hyponatremia with plasma hyposmolality; inappropriately high urine osmolality in the presence of plasma hyposmolality; normal renal and adrenal function; presence of natriuresis despite hyponatremia; no evidence of hypovolemia (e.g., decreased skin turgor, tachycardia), ascites or edema; and correction of hyponatremia with fluid restriction (Reeves et al, 1998). Another supportive criterion is an inappropriately increased plasma AVP concentration in relation to plasma osmolality. However, plasma AVP concentrations are often in the reference range in humans with SIADH and are abnormal only in relation to plasma osmolality (Fig. 1-30), some patients do not have measurably increased plasma AVP concentrations, and most disorders causing solute and volume depletion are associated with appropriately increased plasma AVP concentrations (Robinson and Verbalis, 2011).

Treatment is directed toward alleviation of hyponatremia and elimination of the underlying disease causing SIADH. The goal of treatment directed at the hyponatremia is to correct body water osmolality and restore cell volume to normal by raising the ratio of sodium to water in ECF using IV fluid therapy, water restriction, or both. The increase in ECF osmolality draws water from cells and therefore reduces their volume. Rapid correction of severe hyponatremia can result in demyelination in white matter areas of the brain, a syndrome referred to as osmotic demyelination syndrome, and must be avoided (Verbalis and Martinez, 1991). This pathologic disorder is believed to be precipitated by brain dehydration that occurs after correction of serum sodium concentration towards normal (Sterns et al, 1989). Because loss of brain idiogenic osmoles represents one of the compensatory mechanisms for preserving brain cell volume during dilutional states, an increase in serum sodium concentration toward normal (greater than 140 mEq/L) is relatively hypertonic to brain cells that are partially depleted of idiogenic osmoles as a result of hyponatremia (Sterns et al, 1989; Sterns et al, 1993). Consequently, raising the serum
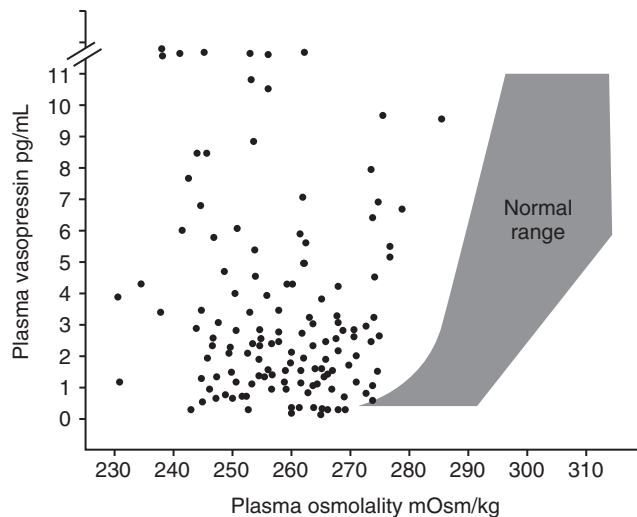

FIGURE 1-30 Plasma arginine vasopressin (AVP) levels in patients with the syndrome of inappropriate antidiuretic hormone (SIADH) secretion as a function of plasma osmolality. Each point depicts one patient at a single point in time. The *shaded area* represents AVP levels in normal subjects over physiologic ranges of plasma osmolality. (Modified from Zerbe RL, Stropes L, Robertson GL: Vasopressin function in the syndrome of inappropriate antidiuresis, *Annu Rev Med* 31:315-327, 1980. In Robertson GL, et al: Neurogenic disorders of osmoregulation, *Am J Med* 72: 339, 1982.)

sodium concentration rapidly to greater than 125 mEq/L can cause demyelination in the CNS (Ayus et al, 1987; Sterns et al, 1994).

Humans and presumably dogs and cats with SIADH are assumed to have chronic hyponatremia, arbitrarily defined as the presence of hyponatremia of less than 130 mEq/L for 48 hours or longer. The current recommendation for correcting severe chronic hyponatremia is to increase the serum sodium concentration slowly at a rate of approximately 0.5 to 1.0 mEq/L per hour using intravenously administered normal (0.9%) or hypertonic (3% to 5%) saline. Adjustments in the rate of fluid administration or composition of the fluid should be based on results of frequent assessment of serum electrolyte concentrations and the patient's CNS status. Once the serum sodium concentration is greater than 125 mEq/L, further correction of hyponatremia is accomplished by restricting water intake. Reduction of fluid intake to the point at which urinary and insensible losses induce a negative water balance leads to restoration of normal body fluid volume, reduction in urinary sodium excretion, and increased serum sodium concentration.

Long term treatment of SIADH includes discontinuation of any drugs known to be associated with SIADH and daily restriction of water intake. The approach to water restriction is similar to that used to treat dogs with psychogenic polydipsia (see Psychogenic Polydipsia under Responses to the Modified Water Deprivation Test earlier in this chapter). However, the goal of water restriction for SIADH is to identify a daily water intake that maintains the serum sodium concentration near the lower end of the reference range. Additional treatments for SIADH in humans include agents that interfere with AVP signaling (e.g., demeclocycline) and AVP receptor antagonists (e.g., tolvaptan). There are no reports on the use of demeclocycline for SIADH in dogs or cats. Treatment of a dog with SIADH with tolvaptan (Otsuka Pharmaceuticals) at a dose of 3 mg/kg orally every 12 hours resulted in a marked increase in free-water excretion and significant palliation of clinical signs with no discernible side effects detected over a 3-year treatment period (Fleeman et al, 2000).

HYPODIPSIC HYPERNATREMIA

Hypodipsic hypernatremia is a neurologic disorder causing diminished sensation of thirst and diminished release of AVP in response to osmotic stimulation. Hypodipsic hypernatremia is characterized by chronic hypernatremia in a setting of euvolemia, normal renal function, decreased thirst perception, and a normal renal response to exogenous AVP (Reeves et al, 1998). Despite elevations of serum sodium concentration and ECF osmolalities, affected patients exhibit hypodipsia and an inappropriately dilute urine for the corresponding plasma osmolality. The primary defect in human patients with hypodipsic hypernatremia appears to be an insensitivity of thirst centers and osmoreceptors to osmotic stimuli. Affected patients have a normal response of AVP release, measured either as a rise in urine osmolality or as an increase in plasma AVP levels, to baroreceptor stimulation following volume contraction.

Given the association of a diminished sensation of thirst and a diminished release of AVP in response to osmotic stimulation, it is likely that hypodipsic hypernatremia represents a more or less specific ablation of hypothalamic osmoreceptor function. In humans, hypodipsic hypernatremia has been reported in children as a congenital disease and in adults in association with CNS histiocytosis, pineal tumors, surgery for craniopharyngioma, head trauma, and vascular disturbances (e.g., ischemia, hemorrhage). Necropsy has been performed in six dogs with hypodipsic hypernatremia and revealed hypothalamic dysplasia in a 4½-month-old Dalmatian (Bagley et al, 1993); hydrocephalus in an adult mixed-breed dog (DiBartola et al, 1994); astrogliosis and neuronal degeneration in the region of the hypothalamus and thalamus in a 7-month-old Miniature Schnauzer (Crawford et al, 1984); focal, severe meningoencephalitis in the hypothalamus in a 7-year-old Doberman Pinscher (Mackay and Curtis, 1999); lobar holoprosencephaly in a 9-month-old Miniature Schnauzer (Sullivan et al, 2003); and no identifiable lesions in the anterior, third cerebral ventricular area, hypothalamus or pituitary gland in a 5-month-old Great Dane (Hawks et al, 1991). Results of an MRI of the CNS in a 6-month-old Miniature Schnauzer with hypodipsic hypernatremia revealed dysgenesis of the corpus callosum and other forebrain structures (Miyama et al, 2009). Hypodipsic hypernatremia has also been described in a 14-month-old Miniature Schnauzer (Hoskins and Rothschmitt, 1984), but the dog was still alive at the time of the report. Hypodipsic hypernatremia was also reported in a 7-month-old Domestic Short-Haired cat in which hydrocephalus was identified with CT imaging (Dow et al, 1987).

Interestingly, congenital hypodipsic hypernatremia has been identified most commonly in Miniature Schnauzers.

Dogs and cats typically present to the veterinarian with signs related to hypernatremia (i.e., lethargy, inappetence, weakness, neurologic signs). Consistent findings on physical examination and initial clinical pathology include dehydration, hypernatremia, hyperchloridemia, prerenal azotemia, and urine specific gravities greater than 1.030. Serum sodium concentrations ranged from 168 to 215 mEq/L; consequently, serum osmolalities were markedly increased. The dogs and cat were conscious and adipsic or hypodipsic despite severe hypernatremia and hyperosmolality, findings that strongly support the diagnosis of hypodipsic hypernatremia. The diagnosis was confirmed in one dog by documenting lack of endogenous AVP secretion with worsening hyperosmolality induced by hypertonic saline infusion and marked AVP secretion in response to conjunctival administration of apomorphine (DiBartola et al, 1994).

Treatment is directed toward alleviation of the hypernatremia and, if possible, elimination of the underlying disease. Rapid correction of hypernatremia by administration of hypotonic fluids intravenously is not recommended, because hypernatremia typically has been developing for more than a week and intracellular idiogenic osmoles have been produced within neurons in response to the increased osmolality of the ECF. Rapid reduction of plasma osmolality can result in an intracellular influx of water into neurons, thereby worsening neurologic signs (see Complications of the Modified Water Deprivation Test: Hypertonic Dehydration and Hypernatremia). Forced oral hydration is recommended in humans, but it does not consistently correct the hypernatremia. Addition of water to the food in excess of maintenance requirements and/or forced oral administration of water was beneficial in most, but not all, dogs and the cat with hypodipsic hypernatremia. One dog was clinically healthy 3 years after establishing the diagnosis and initiating water supplementation with food (Miyama et al, 2009). Chlorpropamide, a sulfonylurea drug that augments the antidiuretic effect of low levels of circulating AVP (see Chlorpropamide under Oral Agents (Used in Central Diabetes Insipidus, Partial Central Diabetes Insipidus, Nephrogenic Diabetes Insipidus, and Primary Polydipsia earlier in this chapter), has been useful in restoring osmotic homeostasis in humans with hypodipsic hypernatremia (Reeves et al, 1998). Chlorpropamide (33 mg/kg/day for 2 weeks) was ineffective in stimulating thirst or correcting hypernatremia in one dog (Crawford et al, 1984). Patients with neurologic signs induced by severe hypernatremia may require intensive fluid therapy to initially control the hypernatremia.

REFERENCES

Abe T: Lymphocytic infundibulo-neurohypophysitis infundibulopanhypophysitis regarded as lymphocytic hypophysitis variant, *Brain Tumour Pathol* 25(2):59, 2008.

Aroch I, et al.: Central diabetes insipidus in five cats: clinical presentation, diagnosis and oral desmopressin therapy, *J Fel Med Surg* 7:333, 2005.

Aron DC, et al.: Hypothalamus and pituitary. In Greenspan FS, Gardner DG, editors: *Basic and clinical endocrinology*, New York, 2001, McGraw Hill, p 100.

Authement JM, et al.: Transient, traumatically induced, central diabetes insipidus in a dog, *J Am Vet Med Assoc* 194:683, 1989.

Ayus JC, et al.: Treatment of symptomatic hyponatremia and its relation to brain damage: a prospective study, *N Engl J Med* 317:1190, 1987.

Bagley RS, et al.: Hypernatremia, adipsia, and diabetes insipidus in a dog with hypothalamic dysplasia, *JAAHA* 29:267, 1993.

Barsanti JA, et al.: Diagnostic approach to polyuria and polydipsia. In Bonagura JD, editor: *Current veterinary therapy XIII*, Philadelphia, 2000, WB Saunders, p 831.

Baylis PH, Robertson GL: Vasopressin function in familial cranial diabetes insipidus, *Postgrad Med J* 57:36, 1981.

Baylis PH, Thompson CJ: Osmoregulation of vasopressin secretion and thirst in health and disease, *Clin Endocrinol* 29(5):549, 1988.

Bhan GL, O'Brien TD: Autoimmune endocrinopathy associated with diabetes insipidus, *Postgrad Med J* 58:165, 1982.

Bichet DG: Nephrogenic diabetes insipidus, *Semin Nephrol* 26:224, 2006.

Biewenga WJ, et al.: Osmoregulation of systemic vasopressin release during long-term glucocorticoid excess: a study in dogs with hyperadrenocorticism, *Acta Endocrinol* 124:583, 1991.

Block LH, et al.: Changes in tissue sensitivity to vasopressin in hereditary hypothalamic diabetes insipidus, *Klin Wochenschr* 59:831, 1981.

Breitschwerdt EB, et al.: Nephrogenic diabetes insipidus in three dogs, *J Am Vet Med Assoc* 179:235, 1981.

Brown BA, et al.: Evaluation of the plasma vasopressin, plasma sodium, and urine osmolality response to water restriction in normal cats and a cat with diabetes insipidus [abstract], *J Vet Intern Med* 7:113, 1993.

Burnie AG, Dunn JK: A case of central diabetes insipidus in the cat: diagnosis and treatment, *J Small Anim Pract* 23:237, 1982.

Cameron K, Gallagher A: Syndrome of inappropriate antidiuretic hormone secretion in a cat, *J Am Anim Hosp Assoc* 46:425, 2010.

Capen CC, Martin SL: Diseases of the pituitary gland. In Ettinger SJ, editor: *Textbook of veterinary internal medicine*, ed 2, Philadelphia, 1983, WB Saunders, p 1523.

Crawford MA, et al.: Hypernatremia and adipsia in a dog, *J Am Vet Med Assoc* 184:818, 1984.

Cronin RE: Psychogenic polydipsia with hyponatremia: report of eleven cases, *Am J Kidney Dis* 4:410, 1987.

Davenport DJ, et al.: Diabetes insipidus associated with metastatic pancreatic carcinoma in a dog, *J Am Vet Med Assoc* 189:204, 1986.

Deppe TA, et al.: Glomerular filtration rate and renal volume in dogs with congenital portosystemic vascular anomalies before and after surgical ligation, *J Vet Int Med* 13:465, 1999.

DiBartola SP, et al.: Hypodipsic hypernatremia in a dog with defective osmoregulation of antidiuretic hormone, *J Am Vet Med Assoc* 204:922, 1994.

Dillingham MA, Anderson RJ: Inhibition of vasopressin action by atrial natriuretic factor, *Science* 231:1572, 1986.

Dow SW, et al.: Hypodipsic hypernatremia and associated myopathy in a hydrocephalic cat with transient hypopituitarism, *J Am Vet Med Assoc* 191:217, 1987.

Edwards DF, et al.: Hypernatremic, hypertonic dehydration in the dog with diabetes insipidus and gastric dilatation volvulus, *J Am Vet Med Assoc* 182:973, 1983.

Feldman BJ, et al.: Nephrogenic syndrome of inappropriate antidiuresis, *N Engl J Med* 352:1884, 2005.

Ferring AB: *Product Information, DDAVP*, Malmo, 1985, Sweden.

Fleeman LM, et al.: Effects of an oral vasopressin receptor antagonist (OPC-31260) in a dog with syndrome of inappropriate secretion of antidiuretic hormone, *Aust Vet J* 78:825, 2000.

Fujisawa I: Magnetic resonance imaging of the hypothalamic-neurohypophyseal system, *J Neuroendocrinol* 16:297, 2004.

Goldman MB, et al.: Mechanisms of altered water metabolism in psychotic patients with polydipsia and hyponatremia, *N Engl J Med* 318:397, 1988.

Goossens MMC, et al.: Central diabetes insipidus in a dog with a pro-opiomelanocortin-producing pituitary tumor not causing hyperadrenocorticism, *J Vet Int Med* 9:361, 1995.

Grunbaum EG, Moritz A: Zur diagnostik des diabetes insipidus renalis beim hund, *Tierarztliche Praxis* 19:539, 1991.

Grunbaum EG, et al.: Genetisch bedingter diabetes insipidus renalis beim hund. 35th Annual Meeting, Deutsche Veterinarmedizinische Gesellschaft DVG, Fachgeruppe Kleintierkrankheiten (ed. DVG), DVG, GieBen FRG, 1990, p. 126.

Hanson JM, et al.: Efficacy of transsphenoidal hypophysectomy in treatment of dogs with pituitary-dependent hyperadrenocorticism, *J Vet Intern Med* 19: 687, 2005.

Harb M, et al.: Central diabetes insipidus: 20 dogs (1986-1995), *J Am Vet Med Assoc* 209:1884, 1996.

Hardy RM: Disorders of water metabolism, *Vet Clin North Am Small Anim Pract* 12(3):353, 1982.

Hardy RM, Osborne CA: Water deprivation test in the dog: maximal normal values, *J Am Vet Med Assoc* 174:479, 1979.

Hawks D, et al.: Essential hypernatremia in a young dog, *J Small Anim Pract* 32:420, 1991.

Heiene R, et al.: Vasopressin secretion in response to osmotic stimulation and effects of desmopressin on urinary concentrating capacity in dogs with pyometra, *Am J Vet Res* 65(4):404, 2004.

Hoskins JD, Rothschmitt J: Hypernatremic thirst deficiency in a dog, *Vet Med* 79:489, 1984.

Houston DM, et al.: Syndrome of inappropriate antidiuretic hormone secretion in a dog, *Can Vet J* 30:423, 1989.

Kamoi K: Syndrome of inappropriate antidiuresis without involving inappropriate secretion of vasopressin in an elderly woman: effect of intravenous administration of the nonpeptide vasopressin V_2 receptor antagonist OPC-31260, *Nephron* 76:111, 1997.

Kang MH, Park HM: Syndrome of inappropriate antidiuretic hormone secretion concurrent with liver disease in a dog, *J Vet Med Sci* 74:645, 2012.

Kaplowitz PB, et al.: Radioimmunoassay of vasopressin in familial central diabetes insipidus, *J Pediatr* 100:76, 1982.

Kraus KH: The use of desmopressin in diagnosis and treatment of diabetes insipidus in cats, *Compend Cont Educ Small Anim Pract* 9:752, 1987.

Kurokawa H, et al.: Postserior lobe of the pituitary gland: correlation between signal intensity on T1-weighted M images and vasopressin concentration, *Radiology* 207:79, 1998.

Kusano E, et al.: Chlorpropamide action on renal concentrating mechanism in rats with hypothalamic diabetes insipidus, *J Clin Invest* 72:1298, 1983.

Lam KS, et al.: Pharmacokinetics, pharmacodynamics, long-term efficacy and safety of oral 1-deamino-8-D-arginine vasopressin in adult patients with central diabetes insipidus, *Br J Clin Pharmacol* 42(3):379, 1996.

Lantz GC, et al.: Transsphenoidal hypophysectomy in the clinically normal dog, *Am J Vet Res* 49:1134, 1988.

Lee J, et al.: Atrial natriuretic factor inhibits vasopressin secretion in conscious sheep, *Proc Soc Exp Biol Med* 185:272, 1987.

Luzius H, et al.: A low affinity vasopressin V_2 receptor in inherited nephrogenic diabetes insipidus, *J Receptor Res* 12:351, 1992.

Mackay BM, Curtis N: Adipsia and hypernatremia in a dog with focal hypothalamic granulomatous meningoencephalitis, *Aust Vet J* 77:14, 1999.

Maghnie M, et al.: Persistent high MR signal of the posterior pituitary gland in central diabetes insipidus, *J Neuroradiol* 18:1749, 1997.

Marver D: Evidence of corticosteroid action along the nephron, *Am J Physiol* 246:F111, 1984.

Meij BP, et al.: Lymphocytic hypophysitis in a dog with diabetes insipidus, *J Comp Path* 147:503, 2012.

Miyama TS, et al.: Magnetic resonance imaging and clinical findings in a Miniature Schnauzer with hypodipsic hypernatremia, *J Vet Med Sci* 71:1387, 2009.

Moses AM, Clayton B: Impairment of osmotically stimulated AVP release in patients with primary polydipsia, *Am J Physiol* 265:R1247, 1993.

Moses AM, et al.: Use of T1-weighted MR imaging to differentiate between primary polydipsia and central diabetes insipidus, *Am J Neuroradiol* 13(5):1373, 1992.

Neer TM, Reavis DU: Craniopharyngioma and associated central diabetes insipidus and hypothyroidism in a dog, *J Am Vet Med Assoc* 182:519, 1983.

Oliveira KM, et al.: Head trauma as a possible cause of central diabetes insipidus in a cat, *J Fel Med Surg* 15:155, 2013.

Papanek PE, Raff H: Chronic physiological increases in cortisol inhibit the vasopressin response to hypertonicity in conscious dogs, *Am J Physiol* 267:R1342, 1994.

Papanek PE, et al.: Corticosterone inhibition of osmotically stimulated vasopressin from hypothalamic-neurohypophysial explants, *Am J Physiol* 272:R158, 1997.

Peterson ME, et al.: Acromegaly in 14 cats, *J Vet Intern Med* 4:192, 1990.

Pittari JM: Central diabetes insipidus in a cat, *Feline Pract* 24:18, 1996.

Pollock AS, Arieff AI: Abnormalities of cell volume and their functional consequence, *Am J Physiol* 239:F195, 1980.

Post K, et al.: Congenital central diabetes insipidus in two sibling Afghan Hound pups, *J Am Vet Med Assoc* 194:1086, 1989.

Quinkler M, Stewart PM: Hypertension and the cortisol-cortisone shuttle, *J Clin Endocrinol Metab* 88:2384, 2003.

Ramsay DJ: Posterior pituitary gland. In Greenspan FS, Forsham PH, editors: *Basic and clinical endocrinology*, Los Altos, CA, 1983, Lange Medical Publications, p 120.

Reeves WB, et al.: The posterior pituitary and water metabolism. In Wilson JD, Foster DW, Kronenberg HM, Larsen PR, editors: *Williams textbook of endocrinology*, ed 9, Philadelphia, 1998, WB Saunders, p 341.

Reidarson TH, et al.: Extreme hypernatremia in a dog with central diabetes insipidus: a case report, *JAAHA* 26:89, 1990.

Richardson DW, Robinson AG: Desmopressin, *Ann Intern Med* 103:228, 1985.

Rijnberk A, et al.: Inappropriate vasopressin secretion in two dogs, *Acta Endocrinol* 117:59, 1988.

Rijnberk A, et al.: Aldosteronoma in a dog with polyuria as the leading symptom, *Domest Anim Endocrinol* 20:227, 2001.

Robben JH, et al.: Cell biological aspects of the vasopressin type-2 receptor and aquaporin 2 channel in nephrogenic diabetes insipidus, *Am J Physiol Renal Physiol* 291:F257, 2006.

Robertson GL: Diseases of the posterior pituitary. In Felig P, et al.: *Endocrinology and metabolism*, New York, 1981, McGraw Hill, p 251.

Robertson GL: Differential diagnosis of polyuria, *Ann Rev Med* 39:425, 1988.

Robertson GL, Scheidler JA: A newly recognized variant of familial nephrogenic diabetes insipidus distinguished by partial resistance to vasopressin (type 2) [abstract], *Clin Res* 29:555A, 1981.

Robinson AG: DDAVP in the treatment of central diabetes insipidus, *N Engl J Med* 294:507, 1976.

Robinson AG, Verbalis G: Posterior pituitary. In Melmed S, Polonsky K, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Elsevier, p 291.

Saeki N, et al.: MRI of ectopic posterior pituitary bright spot with large adenomas: appearances and relationship to transient postoperative diabetes insipidus, *Neuroradiology* 45:713, 2003.

Salvi M, et al.: Role of autoantibodies in the pathogenesis and association of endocrine autoimmune disorders, *Endocr Rev* 9:450, 1988.

Sands JM, Bichet DG: Neprogenic diabetes insipidus, *Ann Intern Med* 144:186, 2006.

Scherbaum WA: Role of autoimmunity in hypothalamic disorders, *Bailliere's Clin Immunol* 1:237, 1987.

Scherbaum WA, et al.: Autoimmune cranial diabetes insipidus: its association with other endocrine diseases and with histiocytosis X, *Clin Endocrinol* 25:411, 1986.

Schwartz J, et al.: Hemodynamic effects of neurohypophyseal peptides with antidiuretic activity in dogs, *Am J Physiol* 249:H1001, 1985.

Schwartz Porsche D: Diabetes insipidus. In Kirk RW, editor: *Current veterinary therapy VII*, Philadelphia, 1980, WB Saunders, p 1005.

Scollan KF, et al.: Validation of a commercially available enzyme immunoassay for measurement of plasma antidiuretic hormone concentration in healthy dogs and assessment of plasma antidiuretic hormone concentration in dogs with congestive heart failure, *Am J Vet Res* 74:1206, 2013.

Spanakis E, et al.: AVPR2 variants and mutations in nephrogenic diabetes insipidus: review and missense mutation significance, *J Cell Physiol* 217:605, 2008.

Sterns RH, et al.: Brain dehydration and neurologic deterioration after rapid correction of hyponatremia, *Kidney Int* 35:69, 1989.

Sterns RH, et al.: Organic osmolytes in acute hyponatremia, *Am J Physiol* 264:F833, 1993.

Sterns RH, et al.: Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective, *J Am Soc Nephrol* 4:1522, 1994.

Stocker SD, et al.: Role of renin-angiotensin system in hypotension-evoked thirst: studies with hydralazine, *Am J Physiol Regul Integr Comp Physiol* 279:R576, 2000.

Sullivan SA, et al.: Lobar holoprosencephaly in a Miniature Schnauzer with hypodipsic hypernatremia, *J Am Vet Med Assoc* 223:1783, 2003.

Teshima T, et al.: Central diabetes insipidus after transsphenoidal surgery in dogs with Cushing's disease, *J Vet Med Sci* 73:33, 2011.

Thrasher TN: Baroreceptor regulation of vasopressin and renin secretion: low-pressure versus high-pressure receptors, *Front Neuroendocrinol* 15(2):157, 1994.

van Lieburg AF, et al.: Clinical presentation and follow-up of 30 patients with congenital nephrogenic diabetes insipidus, *J Am Soc Nephrol* 10:1958, 1999.

van Vonderen IK, et al.: Polyuria and polydipsia and disturbed vasopressin release in two dogs with secondary polycythemia, *J Vet Int Med* 11:300, 1997a.

van Vonderen IK, et al.: Intra- and interindividual variation in urine osmolality and urine specific gravity in healthy pet dogs of various ages, *J Vet Int Med* 11:30, 1997b.

van Vonderen IK, et al.: Disturbed vasopressin release in four dogs with so-called primary polydipsia, *J Vet Int Med* 13:419, 1999.

van Vonderen IK, et al.: Vasopressin response to osmotic stimulation in 18 young dogs with polyuria and polydipsia, *J Vet Intern Med* 18:800, 2004.

Verbalis JG, Martinez AJ: Neurological and neuropathological sequelae of correction of chronic hyponatremia, *Kidney Int* 39:1274, 1991.

Victor W, et al.: Failure of antipsychotic drug dose to explain abnormal diurnal weight gain among 129 chronically psychotic inpatients, *Prog Neuropsychopharmacol Biol Psychiatry* 13:709, 1989.

Winterbotham J, Mason KV: Congenital diabetes insipidus in a kitten, *J Small Anim Pract* 24:569, 1983.

Zerbe RL, Robertson GL: A comparison of plasma vasopressin measurements with a standard indirect test in the differential diagnosis of polyuria, *N Engl J Med* 305:1539, 1981.