CHAPTER

70 The Syndrome of Inappropriate Antidiuretic Hormone Secretion and Other Hypoosmolar Disorders

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The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is produced when plasma levels of arginine vasopressin (AVP), the only known antidiuretic hormone (ADH), are elevated at times when physiologic AVP secretion from the posterior pituitary would normally be suppressed. Because the only clinical abnormality known to result from increased secretion of AVP is a decrease in the osmotic pressure of body fluids, the hallmark of SIADH is hypoosmolality. This clinical finding led to the identification of the first well described cases of this disorder in 1957[1] and the subsequent clinical investigations that resulted in the delineation of the essential characteristics of the syndrome.[2] It is therefore appropriate to begin this chapter with a brief summary of some general issues concerning hypoosmolality and hyponatremia before discussing details that are specific to SIADH and related disorders associated with dilutional hypoosmolality of body fluids. Although much has been learned over the last five decades about the pathophysiology of SIADH and hyponatremia, it remains surprising how rudimentary our understanding is of some of the most basic aspects of this disorder.[3,4] One particularly striking example of this is the controversy concerning the most appropriate rate of correction of hyponatremic patients.[5] Nonetheless, recent and ongoing clinical and basic studies have continued to shed new light on many heretofore incompletely understood aspects of hypoosmolar disorders. In addition, we have begun an exciting new era with regard to the therapy of these disorders using antagonists of AVP receptors.[6] Although some of the specific information contained in this chapter will undoubtedly become outdated in the future, the basic concepts underlying the pathophysiology, diagnosis, and therapy of hypoosmolar disorders have withstood the tests of time and clinical utility, and likely will remain valid for some time to come.

HYPOOSMOLALITY AND HYPONATREMIA

Incidence

Hypoosmolality is one of the most common disorders of fluid and electrolyte balance encountered in hospitalized patients. The incidence and prevalence of hypoosmolar disorders depend on the nature of the patient population being studied as well as on the laboratory methods and diagnostic criteria used to ascertain hyponatremia. Most investigators have used the serum sodium concentration ($[Na^+]$) to determine the clinical incidence of hypoosmolality. When hyponatremia is defined as a serum $[Na^+]$ of less than 135 mEq per L, incidences as high as 15% to 30% have been observed in studies of both acutely and chronically[7,8] hospitalized patients. These high incidences in hospitalized patients are corroborated by frequency analysis of a large population of hospitalized patients, which demonstrated that serum $[Na^+]$ and chloride concentrations were approximately 5 mEq per L lower than those in a control group of healthy, nonhospitalized subjects.[9] However, incidences decrease to the range of 1% to 4% when only patients with serum $[Na^+]$ less than 130 to 131 mEq per L are included,[10–12] which may represent a more appropriate level to define the occurrence of clinically significant cases of this disorder. Even when one uses these more stringent criteria to define hypoosmolality, incidences from 7% to 53% have been reported in institutionalized geriatric patients.[13,14] Perhaps most importantly, reports of all studies to date have noted a high proportion of iatrogenic or hospital-acquired hyponatremia, which has accounted for as much as 40% to 75% of all patients studied.[12,15,16] Therefore, although hyponatremia and hypoosmolality are exceedingly common, most cases are relatively mild and become manifest during the course of hospitalization.

These considerations could be interpreted to indicate that hypoosmolality is of relatively little clinical significance, but this conclusion is unwarranted for several reasons. First, severe hypoosmolality (serum $[Na^+]$ levels <120 mEq per L), although relatively uncommon, is associated with substantial morbidity and mortality.[17,18] Second, even relatively mild hypoosmolality can quickly progress to more dangerous levels during the course of therapeutic management of other disorders. Third, overly rapid correction of hyponatremia can itself cause severe neurologic morbidity and mortality.[19] Finally, it has been observed that mortality

rates are much higher, from threefold[11,20] to 60-fold,[12] in patients with even asymptomatic degrees of hypoosmolality compared to normonatremic patients. Although earlier studies associated increased mortality with serum [Na^+] levels less than130 mEq per L, more recent studies indicate an increased risk of mortality even when serum [Na^+] levels decrease below 137 mEq per L.[15] Remarkably, hyponatremia has been found to represent an independent predictor of worsened outcomes in virtually every disease ever studied, from congestive heart failure to tuberculosis to liver failure.[16] Although this is probably because hypoosmolality is more an indicator of the severity of many underlying illnesses than it is an independent contributing factor to mortality, this presumption may not be true of all cases. These considerations emphasize the importance of a careful evaluation of all hyponatremic patients, regardless of the clinical setting in which they present.

Osmolality, Tonicity, and Serum [Na^+]

As discussed in Chapter 4, the osmolality of body fluid normally is maintained within narrow limits by osmotically regulated AVP secretion and thirst. Although basal plasma osmolality can vary appreciably among individuals, the range in the general population under conditions of normal hydration lies between 275 and 295 mOsm per kg H_2O. Plasma osmolality can be determined directly by measuring the freezing point depression or the vapor pressure of plasma. Alternatively, it can be calculated indirectly from the concentrations of the three major solutes in plasma:

$$\text{Posm (mOsm/kg } H_2O) = 2 \times [Na^+] \text{ (mEq/L)} + \text{glucose (mg/dL)}/18 + \text{blood urea nitrogen (mg/dL)}/2.8$$

Both methods produce comparable results under most conditions. Although either of these methods produces valid measures of total osmolality, this is not always equivalent to the effective osmolality, which is commonly referred to as the tonicity of the plasma. Only cell membrane impermeable solutes such as Na^+ and Cl^- that remain relatively compartmentalized within the extracellular fluid (ECF) space are "effective" solutes, because these solutes create osmotic gradients across cell membranes and thus generate osmotic movement of water from the intracellular fluid (ICF) compartment into the ECF compartment. By contrast, solutes that readily permeate cell membranes (e.g., urea, ethanol, and methanol) are not effective solutes, because they do not create osmotic gradients across cell membranes and thus do not generate water movement between body fluid compartments. Only the concentrations of effective solutes in plasma should be used to ascertain whether clinically significant hyperosmolality or hypoosmolality is present because these are the only solutes that directly affect body fluid distribution.[21]

Sodium and its accompanying anions represent the bulk of the major effective plasma solutes, so hyponatremia and hypoosmolality are usually synonymous. However, there are two important situations in which hyponatremia will not reflect true hypoosmolality. The first is pseudohyponatremia, which is produced by marked elevations of either lipids or proteins in plasma. In such cases the concentration of Na^+ per liter of plasma water is unchanged, but the concentration of Na^+ per liter of plasma is artifactually decreased because of the larger relative proportion of plasma volume that is occupied by the excess lipids or proteins.[22,23] However, the increased protein or lipid will not appreciably increase the total number of solute particles in solution, so the directly measured plasma osmolality will not be significantly affected under these conditions. Measurement of serum [Na^+] by ion-specific electrodes, which is now commonly employed by most clinical laboratories, is less influenced by high concentrations of lipids or proteins than is measurement of serum [Na^+] by flame photometry,[24] although recent reports have demonstrated that such errors can nonetheless still occur when using autoanalyzers that require a dilution of the plasma sample.[25–27]

The second situation in which hyponatremia does not reflect true plasma hypoosmolality occurs when high concentrations of effective solutes other than Na^+ are present in the plasma. The initial hyperosmolality produced by the additional solute causes an osmotic shift of water from the ICF to the ECF, which in turn produces a dilutional decrease in the serum [Na^+]. Once equilibrium between both fluid compartments is achieved, the total effective osmolality remains relatively unchanged. This situation most commonly occurs with hyperglycemia and represents a frequent cause of hyponatremia in hospitalized patients, accounting for up to 10% to 20% of all cases.[12] Misdiagnosis of true hypoosmolality in such cases can be avoided by measuring plasma osmolality directly, or alternatively by correcting the measured serum [Na^+] by 1.6 mEq per L for each 100 mg per dL increase in serum glucose concentration above normal levels.[28] Recent studies have shown a more complex relation between hyperglycemia and serum [Na^+], and have suggested that a more accurate correction factor may be closer to 2.4 mEq per L.[29] When the plasma contains significant amounts of unmeasured solutes, such as osmotic diuretics, radiographic contrast agents, and some toxins (e.g., ethanol, methanol, and ethylene glycol), plasma osmolality cannot be calculated accurately. In these situations, osmolality must be ascertained by direct measurement, although even this method does not yield an accurate measure of the true effective osmolality if the unmeasured solutes are noneffective solutes that permeate cell membranes (e.g., ethanol).

Because of the previously noted considerations, it should be apparent that the determination of whether true hypoosmolality is present can sometimes be difficult. Nevertheless, a straightforward and relatively simple approach will suffice in most cases:

1. The effective plasma osmolality should be calculated from the measured serum [Na^+] and glucose concentration ($2 \times [Na^+] + \text{glucose}/18$); alternatively, the

measured serum [Na^+] can simply be corrected by 1.6 to 2.4 mEq per L for each 100 mg per dL increase in serum glucose concentration greater than normal levels (100 mg per dL).

2. If the calculated effective plasma osmolality is <275 mOsm per kg H_2O, or if the corrected serum [Na^+] is <135 mEq per L, then significant hypoosmolality exists, providing that large concentrations of unmeasured solutes or pseudohyponatremia secondary to hyperlipidemia or hyperproteinemia are not present.
3. To eliminate the latter possibilities, plasma osmolality should also be measured directly in all cases in which the hyponatremia cannot be accounted for by elevated serum glucose levels. Absence of a discrepancy between the calculated and measured total plasma osmolality (<10 mOsm per kg H_2O) will confirm the absence of significant amounts of unmeasured solutes, such as osmotic diuretics, radiocontrast agents, or ethanol; if a significant discrepancy between these measures is found (called an "osmolal gap"[30]), appropriate tests must then be conducted to rule out pseudohyponatremia or to identify possible unmeasured plasma solutes.[21,31,32] Whether significant hypoosmolality exists in the latter case will depend on the nature of the unmeasured solutes; although this determination will not always be possible, the clinician will at least be alerted to uncertainty about the diagnosis of true hypoosmolality.

Pathogenesis of Hypoosmolality

Because water moves freely between the ICF and ECF across most cell membranes, osmolality will always be equivalent in both of these fluid compartments since water distributes between them in response to osmotic gradients. Consequently, total body osmolality must always be the same as both ECF and ICF osmolality. The bulk of body solute is comprised of electrolytes, namely the exchangeable Na^+ (Na^+_E) in the ECF and the exchangeable K^+ (K^+_E) in the ICF along with their associated anions, so total body osmolality will largely be a function of these parameters[33,34]:

$$\begin{aligned} OSM_{ECF} &= OSM_{ICF} \\ &= \text{total body osmolality} \\ &= (\text{ECF solute} + \text{ICF solute}) / \text{body water} \\ &= (2 \times Na^+_E + 2 \times K^+_E + \text{nonelectrolyte solute}) / \text{body water} \end{aligned}$$

Although these calculations represent an oversimplification of complex factors that determine the relative distribution of intracellular and extracellular solutes (there is a revision of the original Edelman equation for predicting serum [Na^+] based on exchangeable body Na^+ and K^+),[35] they are sufficiently accurate for the purpose of predicting changes in serum [Na^+]. By definition, the presence of plasma hypoosmolality indicates a relative excess of water to solute in the ECF. From the preceding equations, it should be apparent that this can be produced either by an excess of body water, resulting in a dilution of remaining body solute, or alternatively by a depletion of body solute, either Na^+ or K^+, relative to the remaining body water. Table 70.1 summarizes the potential causes of hyponatremia categorized according to whether the initiating event is dilution or depletion of body solute. It should be recognized that such a classification represents an obvious oversimplification, because most clinical hypoosmolar states involve significant

70.1 Pathogenesis of Hypoosmolar Disorders

Depletion (Primary Decreases in Total Body Solute and Secondary Water Retention)
- Renal Solute Loss
  - Diuretic use
  - Solute diuresis (glucose, mannitol)
  - Salt wasting nephropathy
  - Mineralocorticoid deficiency or resistance
- Nonrenal Solute Loss
  - Gastrointestinal (diarrhea, vomiting, pancreatitis, bowel obstruction)
  - Cutaneous (sweating, burns)
  - Blood loss

Dilution (Primary Increases in Total Body Water and Secondary Solute Depletion)
- Impaired Renal Free Water Excretion
  - Increased Proximal Reabsorption
    - Hypothyroidism
  - Impaired Distal Dilution
    - Syndrome of inappropriate antidiuretic hormone secretion
    - Glucocorticoid deficiency
  - Combined Increased Proximal Reabsorption and Impaired Distal Dilution
    - Congestive heart failure
    - Cirrhosis
    - Nephrotic syndrome
- Decreased Urinary Solute Excretion
  - Beer potomania
  - Very low protein diet
- Excess Water Intake
  - Primary polydipsia
  - Dilute infant formula
  - Fresh water drowning

components of both solute depletion and water retention. Nonetheless, it is conceptually useful as a starting point for understanding the mechanisms underlying the pathogenesis of hypoosmolality and as a framework for discussions of therapy of hypoosmolar disorders.

Solute Depletion

Depletion of body solute can result from any significant losses of ECF. Whether via renal or nonrenal routes, body fluid losses by themselves rarely cause hypoosmolality because excreted or secreted body fluids are usually isotonic or hypotonic relative to plasma and therefore tend to increase plasma osmolality. Consequently, when hypoosmolality accompanies ECF losses it is generally the result of replacement of body fluid losses by more hypotonic solutions, thereby diluting the remaining body solutes. This often occurs when patients drink water or other hypotonic fluids in response to ongoing solute and water losses, and also when hypotonic intravenous fluids are administered to hospitalized patients.[36] When the solute losses are marked, these patients can show all of the obvious signs of volume depletion (e.g., addisonian crisis). However, such patients often have a more deceptive clinical presentation because their volume deficits may be partially replaced by subsequently ingested or infused fluids. Moreover, they may not manifest signs or symptoms of cellular dehydration because osmotic gradients will draw water into the relatively hypertonic ICF. Therefore, clinical evidence of hypovolemia strongly supports solute depletion as the cause of plasma hypoosmolality, but absence of clinically evident hypovolemia never completely eliminates this as a possibility. Although ECF solute losses are responsible for most cases of depletion-induced hypoosmolality, ICF solute loss can also cause hypoosmolality as a result of osmotic water shifts from the ICF into the ECF.[33] This mechanism likely contributes to some cases of diuretic-induced hypoosmolality in which depletion of total body K^+ often occurs.[37,38]

Water Retention

Despite the obvious importance of solute depletion in some patients, most cases of clinically significant hypoosmolality are caused by increases in total body water rather than by primary loss of extracellular solute. This can occur because of either impaired renal free water excretion or excessive free water intake. However, the former accounts for most hypoosmolar disorders because normal kidneys have sufficient diluting capacity to allow excretion of up to 20 to 30 L per day of free water (see Chapter 4). Intakes of this magnitude are occasionally seen in a subset of psychiatric patients[39,40] but not in most patients, including patients with SIADH in whom fluid intakes average 2 to 3 L per day.[41] Consequently, dilutional hypoosmolality usually is the result of an abnormality of renal free water excretion. The renal mechanisms responsible for impairments in free water excretion can be subgrouped according to whether the major impairment in free water excretion occurs in proximal or distal parts of the nephron, or both (see Table 70.1).

Any disorder that leads to a decrease in glomerular filtration rate (GFR) causes increased reabsorption of both Na^+ and water in the proximal tubule. As a result, the ability to excrete free water is limited because of decreased delivery of tubular fluid to the distal nephron. Disorders causing solute depletion through nonrenal mechanisms (e.g., gastrointestinal fluid losses) also produce this effect. Disorders that cause a decreased GFR in the absence of significant ECF losses are, for the most part, edema-forming states associated with decreased effective arterial blood volume (EABV) and secondary hyperaldosteronism.[42,43] Although these conditions are typified by increased proximal reabsorption of both Na^+ and fluid, it is now clear that in most cases water retention also results from increased distal reabsorption caused by nonosmotic baroreceptor-mediated stimulated increases in plasma AVP levels,[44,45] with the possible exception of hypothyroidism.

Distal nephron impairments in free water excretion are characterized by an inability to dilute tubular fluid maximally. These disorders are usually associated with abnormalities in the secretion of AVP from the posterior pituitary. However, just as depletion-induced hypoosmolar disorders usually include an important component of secondary impairments of free water excretion, so do most dilution-induced hypoosmolar disorders involve significant degrees of secondary solute depletion. This was recognized even before the first clinical description of SIADH from studies of the effects of posterior pituitary extracts on water retention, which demonstrated that renal salt wasting was predominantly a result of the ECF volume expansion produced by the retained water.[46] Therefore, after sustained increases in total body water secondary to inappropriately elevated AVP levels, sufficient secondary solute losses, predominantly as Na^+, occur and can result in further lowering of plasma osmolality. The actual contribution of Na^+ losses to the hypoosmolality of SIADH is variable and depends in part on both the rate and volume of water retention.[47] The major factor responsible for secondary Na^+ losses appears to be renal hemodynamic effects, and specifically the phenomenon of pressure natriuresis and diuresis induced by the volume expansion.[48] However, volume-stimulated hormones such as atrial natriuretic peptide (ANP) are also elevated in response to the water retention of patients with SIADH,[49,50] and it seems likely that these factors also contribute to the secondary natriuresis, possibly via interactions with intrarenal hemodynamic effects.[51] Regardless of the actual mechanisms involved, the solute losses that occur secondary to water retention can be best understood in the context of volume regulation of the ICF and ECF compartments in response to induced hypoosmolality, which is discussed in the next section.

Some dilutional disorders do not fit particularly well into either category. Chief among these is the hyponatremia that sometimes occurs in patients who ingest large volumes

of beer with little food intake for prolonged periods, called "beer potomania."[52,53] Although the volume of fluid ingested may not seem sufficiently excessive to overwhelm renal diluting mechanisms, in these cases free water excretion is limited by very low urinary solute excretion thereby causing water retention and dilutional hyponatremia. A reported case in which hyponatremia occurred in an ovolactovegetarian with a very low protein intake but no beer ingestion is consistent with this pathophysiologic mechanism.[54] However, because most such patients have very low salt intakes as well, it is likely that relative depletion of body Na^+ stores also is a contributing factor to the hypoosmolality in at least some cases.[55]

Adaptation to Hyponatremia: ICF and ECF Volume Regulation

Many studies have indicated that the combined effects of water retention plus urinary solute excretion cannot adequately explain the degree of plasma hypoosmolality observed in patients.[2,56,57] This observation originally led to the theory of cellular inactivation of solute.[2] Simply stated, this theory suggested that as ECF osmolality falls, water moves into cells along osmotic gradients, thereby causing the cells to swell. At some point during this volume expansion, the cells osmotically "inactivate" some of their intracellular solutes as a defense mechanism to prevent continued cell swelling with subsequent detrimental effects on cell function and survival. As a result of this decrease in intracellular osmolality, water then shifts back out of the ICF into the ECF, but at the expense of further worsening the dilution-induced hypoosmolality. Despite the appeal of this theory, its validity has never been demonstrated conclusively in either human or animal studies.

An appealing alternative theory has been suggested by studies of cell volume regulation, in which cell volume is maintained under hypoosmolar conditions by extrusion of potassium rather than by osmotic inactivation of cellular solute.[58,59] Whole brain volume regulation via similar types of electrolyte losses was first described by Yannet in 1940,[60] and has long been recognized as the mechanism by which the brain was able to adapt to hyponatremia and limit brain edema to sublethal levels.[61–63] Following the recognition that low molecular weight organic compounds, called organic osmolytes, also constituted a significant osmotic component of a wide variety of cell types, studies demonstrated the accumulation of these compounds in response to hyperosmolality in both kidney[64] and brain[65] tissue. Multiple groups have now shown that the brain loses organic osmolytes in addition to electrolytes during the process of volume regulation to hypoosmolar conditions in experimental animals[66–69] and human patients.[70] These losses occur relatively quickly (within 24 to 48 hours in rats) and can account for as much as one third of the brain solute losses during hyponatremia.[71] Such coordinate losses of both electrolytes and organic osmolytes from brain tissue enables very effective regulation of brain volume during chronic hyponatremia (Fig. 70.1).[72]

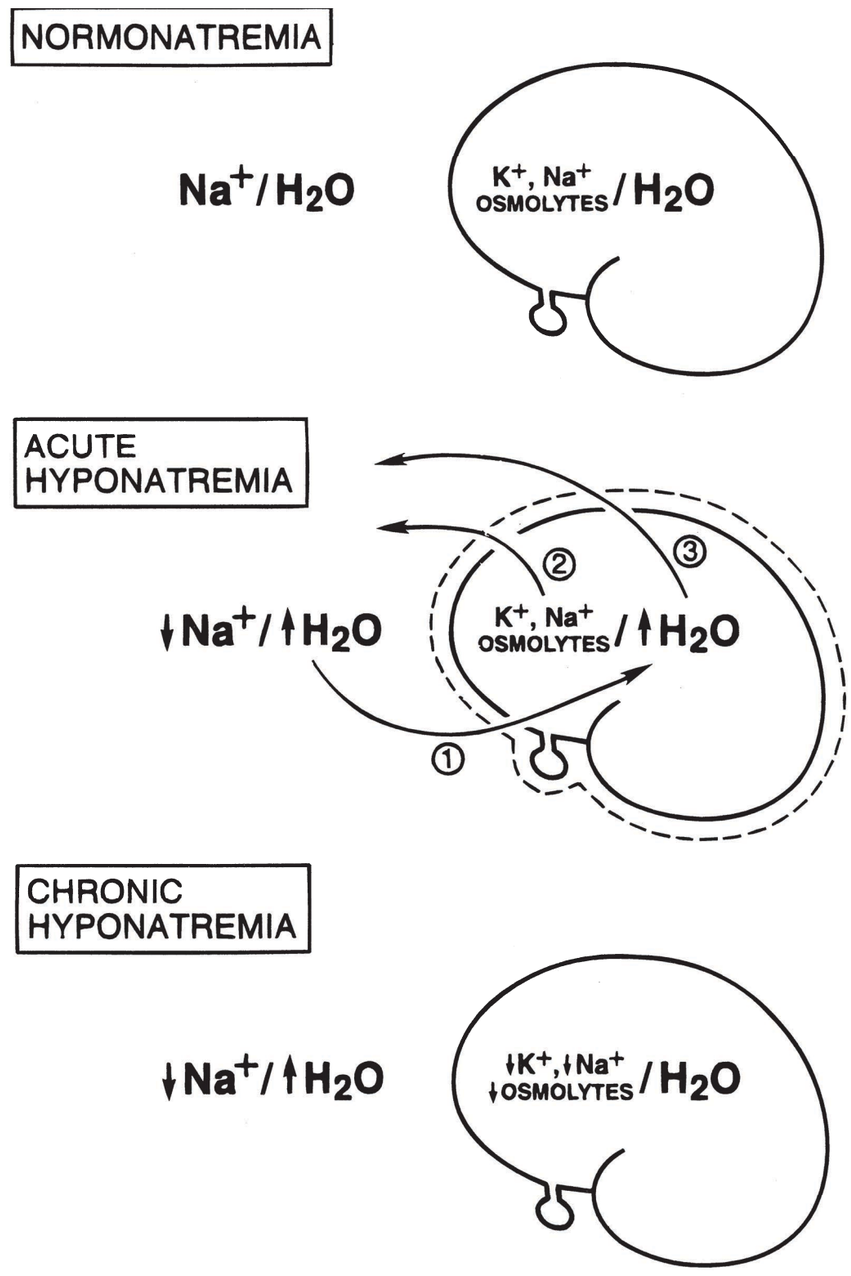

FIGURE 70.1 Schematic diagram of brain volume adaptation to hyponatremia. Under normal conditions brain osmolality and extracellular fluid (ECF) osmolality are in equilibrium (*top panel*; for simplicity the predominant intracellular solutes are depicted as K^+ and organic osmolytes, and the extracellular solute as Na^+). Following the induction of ECF hypoosmolality, water moves into the brain in response to osmotic gradients producing brain edema (*dotted line*, *middle panel*, #1). However, in response to the induced swelling the brain rapidly loses both extracellular and intracellular solutes (*middle panel*, #2). As water losses accompany the losses of brain solute, the expanded brain volume then decreases back toward normal (*middle panel*, #3). If hypoosmolality is sustained, brain volume eventually normalizes completely and the brain becomes fully adapted to the ECF hyponatremia (*bottom panel*).

Consequently, it is now clear that cell volume regulation in vivo in brain tissue occurs predominantly through depletion, rather than intracellular osmotic inactivation, of a variety of intracellular solutes. Ongoing experimental studies are better defining the complex cellular and molecular mechanisms that underlie this profound adaptation to hypoosmolality.

Most studies have focused on volume regulation in the brain during hyponatremia, but all cells volume regulate to varying degrees,[58] and there is little question that this process occurs throughout the body as whole organisms adapt to hypoosmolar conditions. Unexplained components of hyponatremia that led to previous speculation about cellular inactivation of solute are now better explained by cellular losses of both electrolyte and organic solutes as cells throughout the

body undergo volume regulation during hypoosmolar conditions. However, volume regulatory processes are not limited to cells. Although most cases of hyponatremia clearly result from initial water retention induced by stimulated antidiuresis, it has always seemed likely that the resulting natriuresis served the purpose of regulating the volumes of the ECF and intravascular spaces. Many experimental and clinical observations are consistent with ECF volume regulation via secondary solute losses. First, dilutional decreases in concentrations of most blood constituents other than Na^+ and Cl^- do not occur in patients with SIADH,[73] suggesting that their plasma volume is not nearly as expanded as would be predicted simply by the measured decreases in serum [Na^+]. Second, an increased incidence of hypertension has never been observed in patients with SIADH,[74] again arguing against significant expansion of the arterial blood volume. Third, results of animal studies in both dogs[75] and rats[76] have clearly indicated that a significant component of chronic hyponatremia is attributable to secondary Na^+ losses rather than water retention. Furthermore, the relative contributions from water retention versus sodium loss vary with the duration and severity of the hyponatremia: water retention was found to be the major cause of decreased serum [Na^+] in the first 24 hours of induced hyponatremia in rats, but Na^+ depletion then became the predominant etiologic factor after longer periods (7–14 days) of sustained hyponatremia, particularly at very low (<115 mEq per L) serum [Na^+] levels.[76] Finally, multiple studies have attempted to measure body fluid compartment volumes in hyponatremic patients, but without consistent results that indicate either plasma or ECF volume expansion.[1,57,77,78] In particular, a report of body fluid space measurements using isotope dilution techniques in hyponatremic and normonatremic patients with small cell lung carcinoma showed no differences between the two groups with regard to exchangeable sodium space, ECF volume by $^{35}SO_4$ distribution, or total body water.[79] Such results have traditionally been explained by the relative insensitivity of isotope dilution techniques for measurement of body fluid compartment spaces, but an equally plausible possibility is that in the chronically adapted hyponatremic state body fluid compartments have regulated their volumes back toward normal via a combination of extracellular (predominantly electrolyte) and intracellular (electrolyte and organic osmolyte) solute losses.[80] Figure 70.2 schematically illustrates some of the volume regulatory processes that likely occur in response to water retention induced by inappropriate antidiuresis. The degree to which solute losses versus water retention contribute to the resulting hyponatremia will vary in association with many different factors, including the etiology of the hyponatremia, the rapidity of development of the hyponatremia, the chronicity of the hyponatremia, the volume of daily water loading and subsequent volume expansion, and undoubtedly some degree of individual variability as well. It therefore hardly seems surprising that studies of hyponatremic patients have failed to yield uniform results regarding the pathogenesis of hyponatremia in view of the marked diversity of hyponatremic patients and their presentation at different times during the process of adaptation to hypoosmolality via volume regulatory processes.

Differential Diagnosis of Hyponatremia and Hypoosmolality

Because of the multiplicity of disorders causing hypoosmolality and the fact that many involve more than one pathologic mechanism, a definitive diagnosis is not always possible at the time of initial presentation. Nonetheless, a relatively straightforward approach based on the commonly used parameters of ECF volume status and urine sodium concentration generally allows a sufficient categorization of the underlying etiology to allow appropriate decisions regarding initial therapy and further evaluation in most cases (Table 70.2).

Decreased Extracellular Fluid Volume

The presence of clinically detectable hypovolemia nearly always signifies total body solute depletion. A low urine [Na^+] indicates a nonrenal cause of solute depletion. If the urine [Na^+] is high despite hypoosmolality, renal causes of solute depletion are likely responsible. Therapy with thiazide diuretics is the most common cause of renal solute losses,[38] particularly in the elderly,[81,82] but mineralocorticoid deficiency as a result of adrenal insufficiency[83] or mineralocorticoid resistance[84] must always be considered as well. Less commonly, renal solute losses may be the result of a salt-wasting nephropathy (e.g., polycystic kidney disease,[85] interstitial nephritis,[86] or chemotherapy[87]).

Increased Extracellular Fluid Volume

The presence of clinically detectable hypervolemia usually signifies total body Na^+ excess. In these patients, hypoosmolality results from an even greater expansion of total body water caused by a marked reduction in the rate of water excretion (and sometimes an increased rate of water ingestion). The impairment in water excretion is secondary to a decreased EABV,[42,43] which increases the reabsorption of glomerular filtrate not only in the proximal nephron but also in the distal and collecting tubules by stimulating AVP secretion.[44,45] These patients generally have a low urine [Na^+] because of secondary hyperaldosteronism, which is also a product of decreased EABV. However, under certain conditions urine [Na^+] may be elevated, usually secondary to concurrent diuretic therapy but also sometimes because of a solute diuresis (e.g., glucosuria in diabetics) or after successful treatment of the underlying disease (e.g., ionotropic therapy in patients with congestive heart failure). An additional disorder that can produce hypoosmolality and hypervolemia is acute or chronic renal failure with fluid overload[12] (although in early stages of renal failure polyuria from AVP resistance is more likely[88]). Urine [Na^+] in these cases is usually elevated, but it can be variable depending on the stage of renal failure. It is important to remember that primary polydipsia will not be accompanied by signs of hypervolemia because water ingestion alone, in the absence of Na^+ retention, does not typically produce clinically apparent degrees of ECF volume expansion.

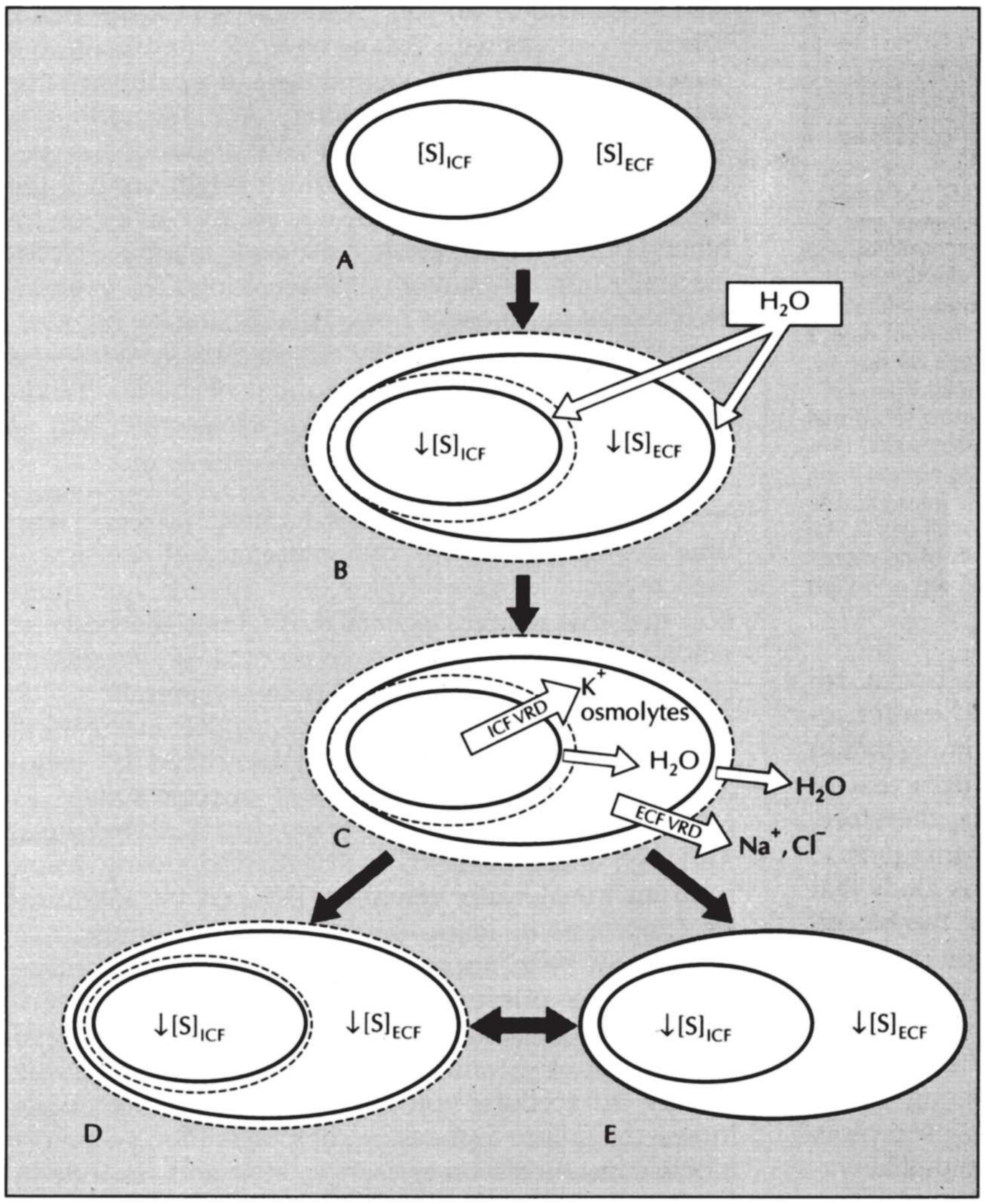

FIGURE 70.2 Schematic illustration of potential changes in whole body fluid compartment volumes at various times during adaptation to hyponatremia. Under basal conditions the concentration of effective solutes in the extracellular fluid ($[S]_{ECF}$) and the intracellular fluid ($[S]_{ICF}$) are in osmotic balance **(A)**. During the first phase of water retention resulting from inappropriate antidiuresis the excess water distributes across total body water, causing expansion of both ECF and ICF volumes (*dotted lines*) with equivalent dilutional decreases in $[S]_{ICF}$ and $[S]_{ECF}$ **(B)**. In response to the volume expansion, compensatory volume regulatory decreases (VRD) occur to reduce the effective solute content of both the ICF (via increased electrolyte and osmolyte extrusion mediated by stretch activated channels and down-regulation of synthesis of osmolytes and osmolyte uptake transporters) and the ECF (via pressure diuresis and natriuretic factors) **(C)**. If both processes go to completion, such as under conditions of fluid restriction, a final steady state can be reached in which ICF and ECF volumes have returned to normal levels but $[S]_{ICF}$ and $[S]_{ECF}$ remain low **(E)**. In most cases this final steady state is not reached, and moderate degrees of ECF and ICF expansion persist, but significantly less than would be predicted from the decrease in body osmolality **(D)**. Consequently, the degree to which hyponatremia is due to dilution from water retention versus solute depletion from volume regulatory processes can vary markedly depending on which phase of adaptation the patient is in, and also on the relative rates at which the different compensatory processes occur (e.g., delayed ICF VRD can worsen hyponatremia due to shifts of intracellular water into the extracellular fluid as intracellular organic osmolytes are extruded and subsequently metabolized, likely accounting for some component of the hyponatremia unexplained by the combination of water retention and sodium excretion in previous clinical studies). (From Verbalis JG. Hyponatremia: epidemiology, pathophysiology, and therapy. *Curr Opin Nephrol Hyperten*. 1993;2:636–652, with permission.)

Normal Extracellular Fluid Volume

Many different hypoosmolar disorders can potentially present clinically with euvolemia, in large part because it is difficult to detect modest changes in volume status using standard methods of clinical assessment; in such cases, measurement of urine $[Na^+]$ is an especially important first step.[89] A high urine $[Na^+]$ in euvolemic patients usually implies a distally mediated, dilution-induced hypoosmolality such as SIADH. However, glucocorticoid deficiency can mimic SIADH so closely that these two disorders are often

70.2 Differential Diagnosis of Hyponatremia

Extracellular Fluid Volume	Urine $[Na^+]$[a]	Presumptive Diagnosis
↓	**Low**	**Depletion (Nonrenal):** gastrointestinal, cutaneous, or blood ECF loss
	High	**Depletion (Renal):** diuretics, mineralocorticoid insufficiency (Addison disease), salt losing nephropathy **Depletion (Nonrenal):** any cause + hypotonic fluid replacement
→	**Low**	**Dilution (Proximal):** hypothyroidism, early decreased effective arterial blood volume **Dilution (Distal):** SIADH, glucocorticoid insufficiency
	High	**Dilution(Distal):** SIADH + fluid restriction **Depletion (Renal):** any cause + hypotonic fluid replacement (especially diuretic treatment)
↑	**Low**	**Dilution (Proximal):** decreased, effective arterial blood volume (congestive heart failure, cirrhosis, nephrosis)
	High	**Dilution (Proximal):** any cause + diuretics or improvement in underlying disease, renal failure

[a]Urine $[Na^+]$ values <30 mEq per L are generally considered to be low and values ≥ 30 mEq per day to be high, based on studies of responses of hyponatremic patients to infusions of isotonic saline.[89]

indistinguishable in terms of water balance.[90,91] Hyponatremia from diuretic use also can present without clinically evident hypovolemia, and the urine $[Na^+]$ will often be elevated in such cases because of the renal tubular effects of the diuretics.[38] Recent studies have suggested that the fractional excretion of uric acid may provide a better measure of ECF volume status in hyponatremic patients on diuretics.[92] A low urine $[Na^+]$ suggests a depletion-induced hypoosmolality from ECF losses with subsequent volume replacement by water or other hypotonic fluids. The solute loss often is generally nonrenal in origin, but an important exception is recent cessation of diuretic therapy, because urine $[Na^+]$ can quickly decrease to low values within 12 to 24 hours after discontinuation of the diuretic. The presence of a low serum $[K^+]$ is an important clue to diuretic use, because few of the other disorders that cause hypoosmolality are associated with significant hypokalemia. However, even in the absence of hypokalemia, any hypoosmolar, clinically euvolemic patient taking diuretics should be assumed to have solute depletion and treated accordingly; subsequent failure to correct the hypoosmolality with isotonic saline administration and persistence of an elevated urine $[Na^+]$ after discontinuation of diuretics then requires reconsideration of a diagnosis of dilutional hypoosmolality. A low urine $[Na^+]$ also can also be seen in some cases of hypothyroidism, in the early stages of decreased EABV before the development of clinically apparent sodium retention and fluid overload, or during the recovery phase from SIADH. Hence, a low urine $[Na^+]$ is less meaningful diagnostically than is a high value.

Because euvolemic causes of hypoosmolality represent the most challenging etiologies of this disease, both in terms of differential diagnosis as well as with regard to the underlying pathophysiology, the subsequent sections will discuss the major causes of euvolemic hypoosmolality and hyponatremia in greater detail.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

SIADH is the most common cause of euvolemic hypoosmolality. It is also the single most prevalent cause of hypoosmolality of all etiologies encountered in clinical practice, with prevalence rates ranging from 20% to 40% among all hypoosmolar patients.[12,41,93,94] The clinical criteria necessary to diagnose SIADH remain basically as set forth by Bartter and Schwartz in 1967.[2] A modified summary of these criteria is presented in Table 70.3 along with several other clinical

70.3 Criteria for the Diagnosis of SIADH

Essential

Decreased effective osmolality of the extracellular fluid (P_{osm} <275 mOsm/kg H_2O)
Inappropriate urinary concentration (U_{osm} >100 mOsm/kg H_2O with normal renal function) at some level of hypoosmolality
Clinical euvolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites)
Elevated urinary sodium excretion while on a normal salt and water intake
Absence of other potential causes of euvolemic hypoosmolality: hypothyroidism, hypocortisolism (Addison disease or pituitary ACTH insufficiency), and diuretic use

Supplemental

Abnormal water load test (inability to excrete at least 90% of a 20 mL/kg water load in 4 hours and/or failure to dilute U_{osm} to <100 mOsm/kg H_2O)
Plasma AVP level inappropriately elevated relative to plasma osmolality
No significant correction of serum [Na^+] with volume expansion but improvement after fluid restriction

findings that support this diagnosis. Several points about each of these criteria deserve emphasis and/or qualification:

1. True hypoosmolality must be present and hyponatremia secondary to pseudohyponatremia or hyperglycemia alone must be excluded.
2. Urinary concentration (osmolality) must be inappropriate for plasma hypoosmolality. This does not mean that urine osmolality must be greater than plasma osmolality (a common misinterpretation of this criterion), but simply that the urine must be less than maximally dilute (i.e., urine osmolality >100 mOsm per kg H_2O). It also should be remembered that urine osmolality need not be elevated inappropriately at all levels of plasma osmolality, because in the reset osmostat variant of SIADH, AVP secretion can be suppressed with resultant maximal urinary dilution and free water excretion if plasma osmolality is decreased to sufficiently low levels.[95,96] Hence, to satisfy the classical criteria for the diagnosis of SIADH, it is necessary only that urine osmolality be inadequately suppressed at some level of plasma osmolality less than 275 mOsm per kg H_2O.
3. Clinical euvolemia must be present to establish a diagnosis of SIADH, because both hypovolemia and hypervolemia strongly suggest different causes of hypoosmolality. This does not mean that patients with SIADH cannot become hypovolemic or hypervolemic for other reasons, but in such cases it is impossible to diagnose the underlying inappropriate antidiuresis until the patient is rendered euvolemic and found to have persistent hypoosmolality.
4. The criterion of renal "salt-wasting" has probably caused the most confusion regarding diagnosis of SIADH. This criterion is included because of its utility in differentiating between hypoosmolality caused by a decreased EABV, in which case renal Na^+ conservation occurs, and distal dilution-induced disorders, in which urinary Na^+ excretion is normal or increased secondary to ECF volume expansion. However, two important qualifications limit the utility of urine [Na^+] measurement in the hypoosmolar patient: urine [Na^+] also is high when solute depletion is of renal origin, as seen with diuretic use or Addison disease, and patients with SIADH can have low urine Na^+ excretion if they subsequently become hypovolemic or solute depleted, conditions that sometimes follow severe sodium and water restriction. Consequently, although a high urine Na^+ excretion is the rule in most patients with SIADH, its presence does not guarantee this diagnosis, and, conversely, its absence does not rule out the diagnosis.
5. The final criterion emphasizes that SIADH remains a diagnosis of exclusion. Thus, the presence of other potential causes of euvolemic hypoosmolality must always be excluded. This includes not only thyroid and adrenal dysfunction, but also diuretic use, because this can also sometimes present as euvolemic hypoosmolality.

Table 70.3 also lists several other criteria that support, but are not essential for a diagnosis of SIADH. The first of these, the water load test, is of value when there is uncertainty regarding the etiology of modest degrees of hypoosmolality in euvolemic patients, but it does not add useful information if the plasma osmolality is <275 mOsm per kg H_2O. Inability to excrete a standard water load normally (with normal excretion defined as a cumulative urine output of at least 90% of the administered water load within 4 hours, and suppression of urine osmolality to <100 mOsm per kg H_2O[97]) confirms the presence of an underlying defect in free water excretion. Unfortunately, water loading is abnormal in almost all disorders that cause hypoosmolality, whether dilutional or depletion-induced with secondary impairments in free water excretion. Two exceptions are primary polydipsia, in which hypoosmolality can rarely be secondary to excessive water intake alone, and the reset osmostat variant of SIADH, in which normal excretion of a water load can occur once plasma osmolality falls below the new set point for AVP secretion. The water load test may also be used

to assess water excretion after treatment of an underlying disorder thought to be causing SIADH. For example, after discontinuation of a drug associated with SIADH in a patient who has already achieved a normal plasma osmolality by fluid restriction, a normal water load test can confirm the absence of persistent inappropriate antidiuresis much more quickly than can simple monitoring of the serum [Na^+] during a period of ad libitum fluid intake. Despite these limitations as a diagnostic clinical test, the water load test remains an extremely useful tool in clinical research for quantitating changes in free water excretion in response to physiologic or pharmacologic manipulations.

The second supportive criterion for a diagnosis of SIADH is an inappropriately elevated plasma AVP level in relation to plasma osmolality. At the time that SIADH was originally described, inappropriately elevated plasma levels of AVP were merely postulated because the measurement of plasma levels of AVP was limited to relatively insensitive bioassays. With the development of sensitive AVP radioimmunoassays capable of detecting the small physiologic concentrations of this peptide that circulate in plasma,[98] there was hope that measurement of plasma AVP levels might supplant the classic criteria and become the definitive test for diagnosing SIADH, as is the case for many syndromes of hormone hypersecretion. This has not occurred for several reasons. First, although plasma AVP levels are elevated in most patients with this syndrome, the elevations generally remain within the normal physiologic range and are abnormal only in relation to plasma osmolality (Fig. 70.3). Therefore, AVP levels can be interpreted only in conjunction with a simultaneous plasma osmolality and knowledge of the relation between AVP levels and plasma osmolality in normal subjects (see Chapter 4). Second, 10% to 20% of patients with SIADH do not have measurably elevated plasma AVP levels; as shown in Figure 70.3, many such patients have AVP levels that are at, or even below, the limits of detection by radioimmunoassay. Whether these cases are true examples of inappropriate antidiuresis in the absence of circulating AVP, or whether they simply represent inappropriate AVP levels that fall below the limits of detection by radioimmunoassay, is not clear. For this reason, Zerbe et al. have proposed using the term SIAD (syndrome of inappropriate antidiuresis) rather than SIADH to describe this entire group of disorders.[99] Studies of hyponatremic children have discovered two genetic mutations of the vasopressin V2 receptor (V2R) that were responsible for constitutive activation of antidiuresis in the absence of AVP-V2R ligand binding.[100] The true incidence of these, and similar V2R mutations, as well as how often they are responsible for patients with SIADH but low or unmeasurable plasma AVP levels, remains to be determined. Third, just as water loading fails to distinguish among various causes of hypoosmolality, so do plasma AVP levels. Many disorders causing solute and volume depletion are associated with elevations of plasma AVP levels secondary to hemodynamic stimuli. For similar reasons, patients with disorders that cause decreased EABV, such as congestive heart failure and cirrhosis, also have elevated AVP levels (see Chapters 67 and 68). Even glucocorticoid insufficiency has been associated with inappropriately elevated AVP levels, as is discussed in the following section.[101] Therefore, multiple different disorders cause stimulation of AVP secretion via nonosmotic mechanisms, rendering this measurement of relatively limited differential diagnostic value. Recent studies using a newly developed assay for copeptin, the glycopeptide C-terminal fragment of the AVP prohormone, have confirmed AVP secretion in most cases of dilutional hyponatremia except for primary polydipsia, where this measurement may prove to be of use diagnostically.[102]

Finally, an improvement in plasma osmolality with fluid restriction but not with volume expansion can sometimes be helpful in differentiating between disorders causing solute depletion and those associated with dilution-induced hypoosmolality. Infusion of isotonic NaCl in patients with SIADH provokes a natriuresis with little correction of osmolality, whereas fluid restriction allows such patients to achieve solute and water balance gradually through insensible free water losses.[1] In contrast, isotonic saline is the treatment of choice in disorders of solute depletion, because once volume deficits are corrected the stimulus to continued AVP secretion and free water retention is eliminated. The diagnostic value of this therapeutic response is limited somewhat by the fact that patients with proximal types of dilution-induced disorders may show a response similar to that found in patients with SIADH. However, the major drawback is that this represents a retrospective test in a situation in which

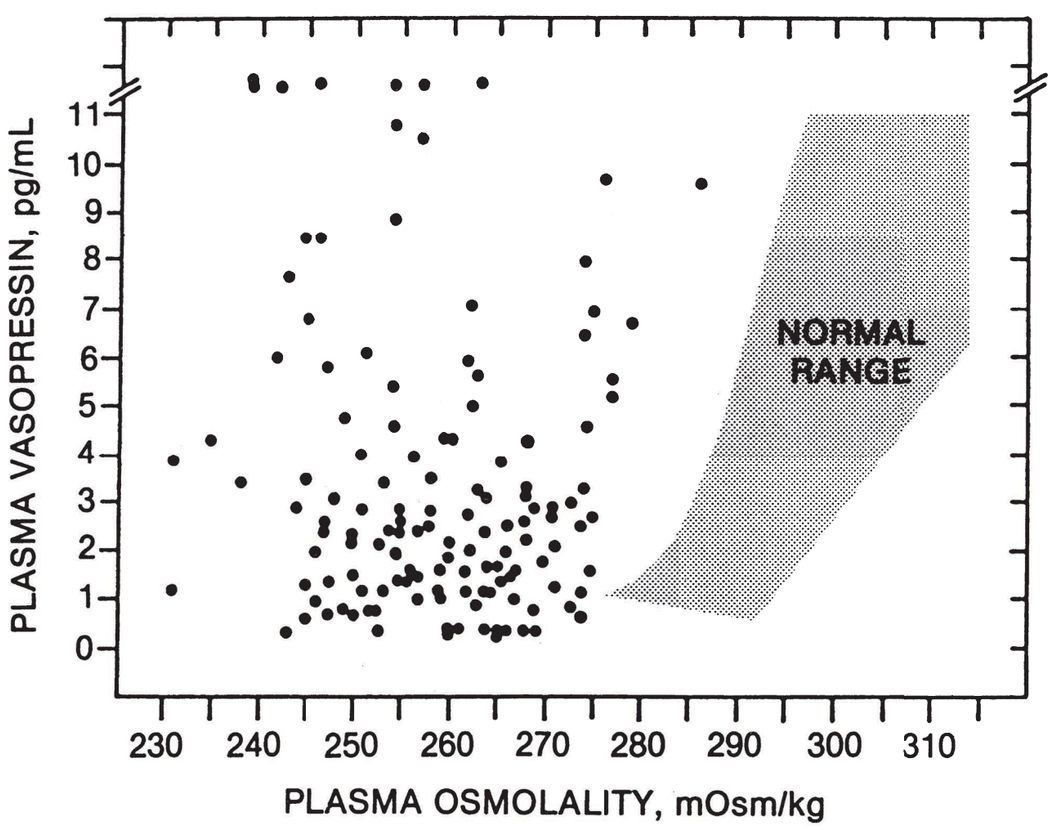

FIGURE 70.3 Plasma AVP levels in patients with SIADH as a function of plasma osmolality. Each point depicts one patient at a single point in time. The *shaded area* represents AVP levels in normal subjects over physiologic ranges of plasma osmolality. The lowest measurable plasma AVP levels using this radioimmunoassay was 0.5 pg per mL. (From Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. *Am J Med.* 1982;72:339–353, with permission.)

it would be preferable to establish a diagnosis before making a decision regarding treatment options. Nonetheless, in difficult cases of euvolemic hypoosmolality, an appropriate therapeutic response can sometimes be helpful in confirming a diagnosis of SIADH.

Etiology

Although the list of disorders associated with SIADH is long, they can be divided into four major etiologic groups (Table 70.4).

Tumors

One of the most common associations of SIADH remains with tumors. Although many different types of tumors have been associated with SIADH (Table 70.4), bronchogenic carcinoma of the lung has been uniquely associated with SIADH since the first description of this disorder in 1957.[1] In virtually all cases, the bronchogenic carcinomas causing this syndrome have been of the small cell variety; a few squamous cell types have been described, but these are rare. Incidences of hyponatremia as high as 11% of all patients with small-cell carcinoma,[103] or 33% of cases with more extensive disease,[104] have been reported. The unusually high incidence of small cell carcinoma of the lung in patients with SIADH, together with the relatively favorable therapeutic response of this type of tumor, makes it imperative that all patients presenting with an otherwise unexplained SIADH be investigated thoroughly and aggressively for a possible tumor. The evaluation should include a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the thorax. In cases with a high degree of suspicion (e.g., hyponatremia in a young smoker) bronchoscopy with cytologic analysis of bronchial washings should be considered even if the results of routine chest radiography are normal, since several studies have reported hypoosmolality that predated any radiographically evident abnormality in patients who then were found to harbor bronchogenic carcinomas 3 to 12 months later.[105,106] Head and neck cancers account for another group of malignancies associated with relatively higher incidences of SIADH,[107] and some of these tumors have clearly been shown to be capable of synthesizing AVP ectopically.[108] A report from a large cancer hospital showed an incidence of hyponatremia for all malignancies combined of 3.7%, with approximately one third of these due to SIADH.[20]

Central Nervous System Disorders

The second major etiologic group of disorders causing SIADH has its origins in the central nervous system (CNS). Despite the large number of different CNS disorders associated with SIADH, there is no obvious common denominator linking them. However, this is actually not surprising when one considers the neuroanatomy of neurohypophysial innervation. The magnocellular AVP neurons receive excitatory inputs from osmoreceptor cells located in the anterior hypothalamus, but also have a major innervation from brainstem cardiovascular

70.4 Common Etiologies of SIADH

Tumors
Pulmonary/mediastinal (bronchogenic carcinoma; mesothelioma; thymoma)
Non-chest (duodenal carcinoma; pancreatic carcinoma; ureteral/prostate carcinoma; uterine carcinoma; nasopharyngeal carcinoma; leukemia)
Central Nervous System Disorders
Mass lesions (tumors; brain abscesses; subdural hematoma)
Inflammatory diseases (encephalitis; meningitis; systemic lupus; acute intermittent porphyria, multiple sclerosis)
Degenerative/demyelinative diseases (Guillain-Barré; spinal cord lesions)
Miscellaneous (subarachnoid hemorrhage; head trauma; acute psychosis; delirium tremens; pituitary stalk section; transsphenoidal adenomectomy; hydrocephalus)
Drug Induced
Stimulated AVP release (nicotine; phenothiazines; tricyclics)
Direct renal effects and/or potentiation of AVP antidiuretic effects (dDAVP; oxytocin; prostaglandin synthesis inhibitors)
Mixed or uncertain actions (amiodarone; angiotensin converting enzyme inhibitors; carbamazepine and oxcarbazepine; chlorpropamide; clofibrate; clozapine; cyclophosphamide; 3,4-methylenedioxymethamphetamine [ecstasy]; omeprazole; serotonin reuptake inhibitors; vincristine)
Pulmonary Diseases
Infections (tuberculosis; acute bacterial and viral pneumonia; aspergillosis; empyema)
Mechanical/ventilatory (acute respiratory failure; COPD; positive pressure ventilation)
Other
Acquired immunodeficiency syndrome and AIDS-related complex
Prolonged strenuous exercise (marathon; triathlon; ultramarathon; hot-weather hiking)
Chronic inflammation (IL-6)
Senile atrophy
Idiopathic

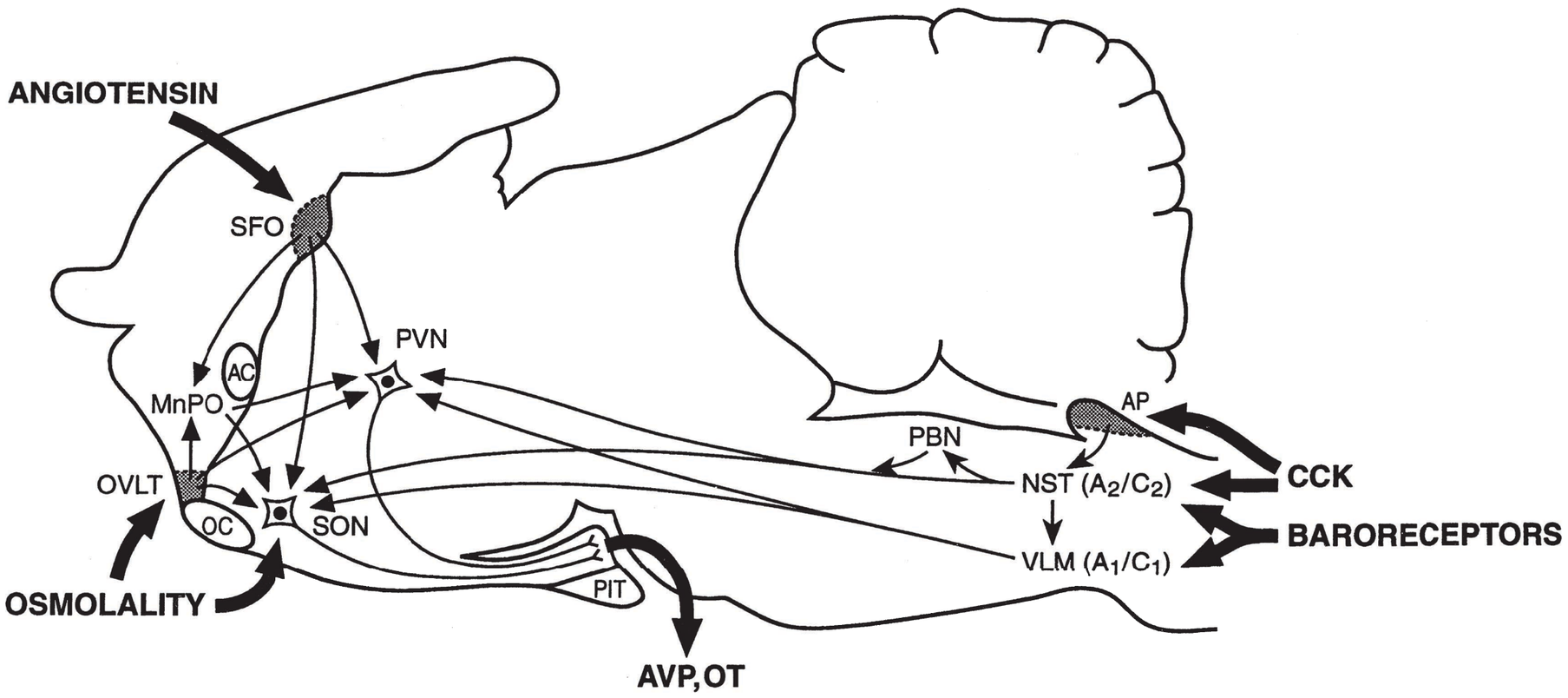

FIGURE 70.4 Diagrammatic summary of the primary brain pathways mediating AVP secretion in response to the major factors that stimulate pituitary AVP secretion. Osmolality activates neurons throughout the anterior hypothalamus, including the SFO and MnPO, but the OVLT appears to be uniquely sensitive to osmotic stimulation and is essential for osmotically stimulated AVP and OT secretion; in addition, osmotic stimulation can act directly on magnocellular neurons which themselves are intrinsically osmosensitive. Similarly, circulating angiotensin II activates cells throughout the OVLT and MnPO, but the SFO appears to be its major and essential site of action. For both of these stimuli, projections from the SFO and OVLT to the MnPO activate both excitatory and inhibitory interneurons that project to the SON and PVN and modulate the direct circumventricular inputs to these areas. Emetic stimuli act both on gastric vagal afferents which terminate in the NST and in some cases also act directly at the AP. Most of the AVP secretion appears to be a result of monosynaptic projections from catecholaminergic A2/C2 cells in the NST. Baroreceptor-mediated stimuli such as hypovolemia and hypotension are considerably more complex. Although they also arise from cranial nerves (IX and X) which terminate in the NST, most experimental data suggest that the major projection to magnocellular AVP neurons arises from catecholaminergic A1 cells of the VLM that are activated by excitatory interneurons from the NST, although some component might also arise from multisynaptic projections through other areas such as the PBN. *AC*, anterior commissure; *AP*, area postrema; *AVP*, arginine vasopressin; *MnPO*, median preoptic nucleus; *NST*, nucleus of the solitary tract; *OC*, optic chiasm; *OT*, oxytocin; *OVLT*, organum vasculosum of the lamina terminalis; *PBN*, parabrachial nucleus; *PIT*, anterior pituitary; *PVN*, paraventricular nucleus; *SFO*, subfornical organ; *SON*, supraoptic nucleus; *VLM*, ventrolateral medulla.

regulatory and emetic centers (Fig. 70.4). Although various components of these pathways have yet to be fully elucidated, many of them appear to have inhibitory as well as excitatory components.[109] Consequently, any diffuse CNS disorder can potentially cause AVP hypersecretion either by nonspecifically exciting these pathways via irritative foci, or alternatively by disrupting them and thereby decreasing the level of inhibition impinging upon the AVP neurons in the neurohypophysis. The wide variety of diverse CNS processes that can potentially cause SIADH stands in contrast to CNS causes of diabetes insipidus, which are for the most part limited to lesions localized to the hypothalamus and/or posterior pituitary that destroy the magnocellular vasopressin neurons (see Chapter 71).

Drugs

Drug-induced hyponatremia is one of the most common causes of hypoosmolality,[110] and may supplant tumors as the most common cause of SIADH. Table 70.4 lists some of the agents that have been associated with SIADH, and new drugs are being continually added to this list.[111] In general, pharmacologic agents cause this syndrome by stimulating AVP secretion, by activating AVP renal receptors to cause antidiuresis, or by potentiating the antidiuretic effect of AVP on the kidney. However, not all of the drug effects associated with inappropriate antidiuresis are fully understood; indeed, many agents may work by means of a combination of mechanisms. For example, chlorpropamide appears to have both a direct pituitary as well as a renal stimulatory effect since it has been reported to increase urine osmolality even in some patients with complete central diabetes insipidus.[112] Agents that cause AVP secretion through solute depletion, such as thiazide diuretics, are not listed here, since these are generally considered to cause depletion-induced hypoosmolality rather than true SIADH. However, some studies have suggested that in some elderly patients the precipitous hyponatremia occasionally seen after administration of thiazide diuretics is caused by polydipsia and water retention more so than by stimulated Na^+ excretion.[113] Whether this represents true SIADH independently of prior ECF volume contraction, as well as whether such cases are typical of a significant portion of patients with diuretic-induced hyponatremia, remains to be determined. A particularly interesting, and clinically important, class of agents associated with SIADH is the selective serotonin reuptake inhibitors (SSRIs). Serotonergic agents have been found to increase AVP secretion in rats in some experimental studies,[114] but most animal studies have suggested more direct

effects on oxytocin rather than AVP secretion.[115] Some studies of SSRIs in humans have failed to show significant effects on AVP secretion,[116] although others support this mechanism.[117] However, hyponatremia following SSRI administration has been reported almost exclusively in the elderly, at rates as high as 22% to 28% in some studies,[118–120] although larger series have suggested an incidence closer to 1 in 200.[121] This therefore suggests the possibility that elderly patients are uniquely hypersensitive to serotonin stimulation of AVP secretion. A similar effect is likely also responsible for the recent reports of severe fatal hyponatremia caused by use of the recreational drug 3,4-methylenedioxymethamphetamine, "ecstasy,"[122,123] because this agent also possesses substantial serotonergic activity.[124] Studies of cFos expression in rats indicate that ecstasy appears to activate hypothalamic magnocellular neurons,[125] suggesting direct effects on AVP secretion as the etiology of the SIADH, and recent studies in humans support this mechanism.[126,127]

Pulmonary Disorders

Pulmonary disorders represent a relatively common but frequently misunderstood cause of SIADH. A variety of pulmonary disorders have been associated with this syndrome, but other than tuberculosis,[128] acute pneumonia,[129–131] and advanced chronic obstructive lung disease,[132] the occurrence of hypoosmolality has been noted mainly in sporadic case reports. Some bacterial infections appear to be associated with a higher incidence of hyponatremia, particularly Legionella pneumoniae.[133] Although one case of pulmonary tuberculosis has been reported that suggested the possibility that tuberculous lung tissue might synthesize AVP ectopically,[134] several other studies have reported that advanced pulmonary tuberculosis is associated with the reset osmostat form of SIADH,[96,128] presumably from nonosmotic stimulation of posterior pituitary AVP secretion. Most cases of pulmonary SIADH not associated with either tuberculosis or pneumonitis have occurred in the setting of respiratory failure. Although hypoxia has clearly been shown to stimulate AVP secretion in animals,[135,136] it appears to be less effective as a stimulus in humans,[137] in whom the stimulus to abnormal water retention appears to be hypercarbia more so than hypoxia.[138,139] When such patients were evaluated serially, the inappropriate AVP secretion was found to be limited to the initial days of hospitalization, when respiratory failure was most marked.[140] Even cases of tubercular SIADH generally have occurred in patients with far advanced, active, pulmonary tuberculosis, although interestingly hyponatremia was also found in 74% of a series of patients with miliary tuberculosis.[141] Therefore, SIADH in non-tumor-related pulmonary disease generally conforms to the following characteristics: (1) the pulmonary disease will always be obvious as a result of severe dyspnea or extensive radiographically evident infiltrates, and (2) the inappropriate antidiuresis will usually be limited to the period of respiratory failure—once clinical improvement has begun, free water excretion generally improves rapidly. Mechanical ventilation can cause inappropriate AVP secretion, or it can worsen any SIADH caused by other factors. This phenomenon has been associated most often with continuous positive pressure ventilation,[142] but it can also occur to a lesser degree with the use of positive end expiratory pressure.

Other Causes

One of the most recently described causes of hypoosmolality is the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC), in patients with human immunodeficiency virus (HIV) infection, with incidences of hyponatremia reported as high as 30% to 38% in adults[143–145] and children.[146] Although there are many potential etiologies for hyponatremia in patients with AIDS/ARC, including dehydration, adrenal insufficiency, and pneumonitis, from 12% to 68% of AIDS patients who develop hyponatremia appear to meet criteria for a diagnosis of SIADH.[143–145] Not unexpectedly, reports have implicated some of the medications used to treat these patients as the cause of the hyponatremia, either via direct renal tubular toxicity or SIADH.[147,148]

A recent series of reports have documented a surprisingly high incidence of hyponatremia during endurance exercise events such as marathon[149] and ultramarathon[150] foot races, triathlons,[151] forced marching,[152] and hiking.[153] Occasionally, this has caused fatal outcomes associated with hyponatremic encephalopathy from acute brain edema.[154,155] Most studies support excess drinking during the exercise as the major cause of the induced hyponatremia,[156,157] but it now appears that water retention under such conditions is also contributed to by SIADH as a result of multiple potential nonosmotic stimuli (e.g., volume depletion, nausea, increased cytokine levels).[158,159]

Unexplained or idiopathic causes account for a relatively small proportion of all cases of SIADH. Although the etiology of the syndrome may not be diagnosed initially in many cases, the numbers of patients in whom an apparent cause cannot be established after consistent follow-up over time are relatively few. However, an exception to this appears to be elderly patients who sometimes develop SIADH without any apparent underlying etiology.[160–162] Coupled with the significantly increased incidence of hyponatremia in geriatric patients,[7,13,14,93,163,164] this suggests that the normal aging process may be accompanied by abnormalities of regulation of AVP secretion that predispose to SIADH. Such an effect could potentially account for the fact that virtually all causes of drug-induced hyponatremia occur much more frequently in elderly patients.[82,165,166] In several series of elderly patients meeting criteria for SIADH, 40% to 60% remained idiopathic despite rigorous evaluation,[167–169] leading some to conclude that extensive diagnostic procedures were not warranted in such elderly patients if routine history, physical examination, and laboratory evaluation failed to suggest a diagnosis.[167]

Some well-known stimuli of AVP secretion are notable primarily because of their exclusion from Table 70.4. Despite unequivocal stimulation of AVP secretion by nicotine,[170] cigarette smoking has only rarely been associated with SIADH,

and primarily in psychiatric patients who have several other potential causes of inappropriate AVP secretion.[39,171,172] This is in part because of chronic adaptation to the effects of nicotine, but also because the short half-life of AVP in plasma (approximately 15 min in humans[173]) limits the duration of antidiuresis produced by relatively short-lived stimuli such as smoking. Although nausea remains the most potent stimulus to AVP secretion known in man,[174] chronic nausea is rarely associated with hypoosmolality unless accompanied by vomiting with subsequent ECF solute depletion followed by ingestion of hypotonic fluids.[175] Similar to smoking, this is probably attributable to the short half-life of AVP, but also to the fact that most such patients are not inclined to drink fluids under such circumstances. However, hyponatremia can occur when such patients are infused with high volumes of hypotonic fluids. This is likely a factor contributing to the hyponatremia that often occurs in cancer patients who are receiving chemotherapy.[103] Finally, a causal relation between stress and SIADH has often been suggested, but never conclusively established. This underscores the fact that stress, independent of associated nausea, dehydration, or hypotension, is not a major stimulus causing sustained elevations of AVP levels in humans.[176]

Pathophysiology

Sources of Arginine Vasopressin Secretion

Disorders that cause inappropriate antidiuresis secondary to elevated plasma AVP levels can be subdivided into those associated with either paraneoplastic (ectopic) or pituitary AVP hypersecretion. Most ectopic production is from tumors, and there is conclusive, cumulative evidence that tumor tissue can, in fact, synthesize AVP: (1) tumor extracts have been found to possess antidiuretic hormone bioactivity and immunologically recognizable AVP and neurophysin, which is synthesized with AVP as part of a common precursor[177–179]; (2) electron microscopy has revealed that many tumors possess secretory granules; and (3) cultured tumor tissue has been shown to synthesize not only AVP[180] but also the entire AVP prohormone (provasopressin[181,182]). Although it is therefore clear that some tumors can produce AVP, it is not certain that all tumors associated with SIADH do so, because only about half of small cell carcinomas have been found to contain AVP immunoreactivity[183] and many of the tumors listed in Table 70.4 have not been studied as extensively as have bronchogenic carcinomas. The only nonneoplastic disorder that has been reported to possibly cause SIADH by means of ectopic AVP production is tuberculosis. However, this is based on studies of a single patient in whom extracts of tuberculous lung tissue were shown by bioassay to possess antidiuretic activity.[134]

Pituitary Arginine Vasopressin Secretion: Inappropriate Versus Appropriate

In the majority of cases of SIADH the AVP secretion originates from the posterior pituitary. However, this is also true of greater than 90% of all cases of hyponatremia, including patients with hypovolemic and hypervolemic hyponatremia.[12] This raises the question of what exactly is inappropriate AVP secretion[184,185]? It is well known that AVP secretion is most sensitively stimulated by increases in osmolality, but also occurs in response to a wide variety of nonosmotic stimuli, including hypotension, hypovolemia, nausea, hypoglycemia, angiotensin, and probably other stimuli yet to be discovered[186] (see Chapter 4). Consequently, AVP secretion in response to a hypovolemic stimulus such as hemorrhage is clearly physiologically "appropriate," but when it leads to symptomatic hyponatremia from secondary water retention it could be considered to be "inappropriate" for osmotic homeostasis. Despite such semantic difficulties, it is important that the criteria for diagnosing SIADH remain as originally described, specifically excluding other clinical conditions that cause known impairments in free water excretion even when these are mediated by a secondary stimulation of AVP secretion via known physiologic mechanisms (e.g., hypovolemia, hypotension, hypocortisolism, edema-forming states, hypothyroidism, etc.). Without maintaining these distinctions, arguable as some of them may be, the definition of SIADH would become too broad to retain any degree of practical clinical usefulness.

Although measurable plasma AVP levels are found in most patients with SIADH, they are rarely elevated into pathologic ranges in most cases, even those associated with ectopic AVP production from tumors. Rather, in the majority of cases of SIADH plasma AVP levels remain in "normal" physiologic ranges, which only become abnormal under hypoosmolar conditions when plasma AVP levels should be suppressed into unmeasurable ranges (Fig. 70.3). This is important for several reasons. First, the well known vasoconstrictive effects of AVP do not come into play until much higher plasma levels are achieved (20 to 80 pg per mL[187]), whereas maximal antidiuresis is achieved with much lower levels (5 to 10 pg per mL). Consequently, it is unlikely that any of the clinical manifestations of hyponatremia can be ascribed to vasopressor effects of AVP. In this regard, it is particularly worrisome that most animal models of induced hyponatremia have employed pharmacologic doses of AVP, which generally elevate plasma AVP levels well into vasopressor ranges, raising the possibility that some results of previous studies of experimental hyponatremia were due to activation of AVP V_1 vascular and hepatic receptors. Recent results that demonstrate the absence of mortality when hyponatremia is induced in animals using the V_2–selective agonist desmopressin (dDAVP),[63] or using vasopressin infusions that maintain plasma AVP levels at lower ranges,[188] emphasize the need to take potential vasopressor effects of vasopressin into consideration in the interpretation of past and future studies. Second, the presence of "normal" plasma AVP levels, or of only mildly elevated urine osmolalities, cannot be used as arguments against SIADH as an etiology for hyponatremia. Low but nonsuppressible levels of AVP can clearly cause sufficient impairment of free water excretion to

produce hypoosmolality when exogenous fluid intakes are high, as in psychiatric patients with polydipsia.[189] Recent studies of patients with SIADH and hypopituitarism have measured high nonsuppressible levels of urinary aquaporin-2 excretion that correlated with their impaired water excretion, supporting persistent activation of AVP V_2 receptors as the cause of the water retention.[190]

Patterns of Arginine Vasopressin Secretion

Studies of plasma AVP levels in patients with SIADH during graded increases in plasma osmolality produced by hypertonic saline administration have suggested four patterns of secretion (Fig. 70.5): (1) random hypersecretion of AVP; (2) a "reset osmostat" system, whereby AVP is secreted at an abnormally low threshold of plasma osmolality but otherwise displays a normal response to relative changes in osmolality; (3) inappropriate hypersecretion below the normal threshold for AVP release, but normal secretion in response to osmolar changes within normal ranges of plasma osmolality; and (4) low or undetectable plasma AVP levels despite classic clinical characteristics of SIADH.[99,191] The first pattern simply represents unregulated AVP secretion, which is often, but not always, observed in patients exhibiting ectopic AVP production. Resetting of the osmotic threshold for AVP secretion has been well described with volume depletion[192,193] and also has been shown to occur in various edema-forming states, presumably as a result of decreases in EABV.[45,194,195] However, most patients with a reset osmostat are clinically euvolemic.[95,96] It has been suggested that chronic hypoosmolality itself may reset the intracellular threshold for osmoreceptor firing, but studies in animals have not supported a major role for this mechanism since chronic hyponatremia does not appear to significantly alter the osmotic threshold for AVP secretion.[196,197] Perhaps the best-known physiologic example of a reset osmostat for AVP secretion is the hypoosmolality and hyponatremia that occurs during late pregnancy. Despite intensive studies over many years to identify potential hormonal factors that might be responsible for this resetting, a single factor has not yet been identified,[198] although some studies have indicated that the placental hormone relaxin causes a stimulation of AVP and oxytocin secretion that closely resembles the reset osmostat pattern of AVP secretion.[199,200] Perhaps the most perplexing aspect of the reset osmostat pattern is its occurrence in patients with tumors, which suggests that some of these cases represent tumor-stimulated pituitary AVP secretion rather than paraneoplastic AVP secretion.[99,191,201] The pattern of SIADH that occurs without measurable AVP secretion is not yet well understood. This form of the syndrome may be attributable to the secretion of AVP with some bioactivity but altered immunoreactivity, to the presence of other circulating antidiuretic factors, to increased renal sensitivity to very low circulating levels of AVP, or possibly to constitutively activating mutations of the AVP V_2 receptor.[100] A sufficient number of patients with this form of the disorder has not been studied to form any basis for discrimination among these possibilities, but the positive response of one such patient to a vasopressin V_2-receptor antagonist suggests that at least some of these cases may represent increased renal sensitivity to low circulating levels of AVP.[202] Despite these well-described patterns of abnormal AVP secretion in SIADH, it is surprising that no correlation has been found between any of these four patterns and the various etiologies of the syndrome.[99]

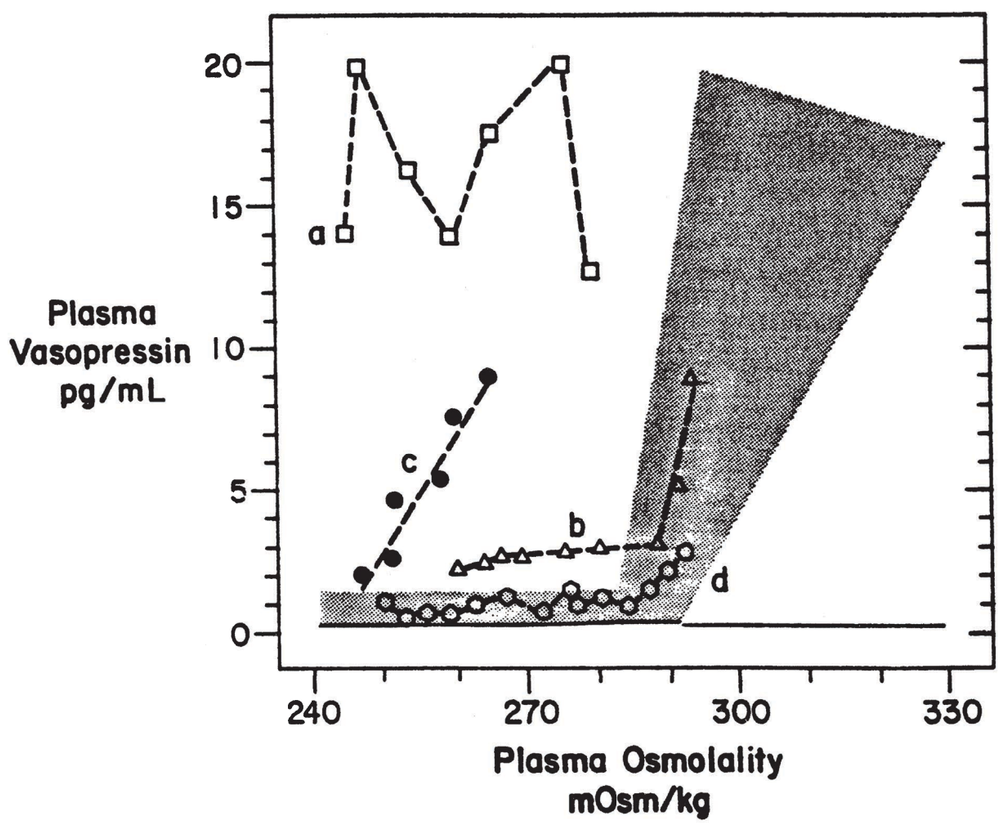

FIGURE 70.5 Schematic summary of different patterns of AVP secretion in patients with SIADH. Each line *(a–d)* represents the relation between plasma AVP and plasma osmolality of individual patients in whom osmolality was increased by infusion of hypertonic NaCl. The *shaded area* represents plasma AVP levels in normal subjects over physiologic ranges of plasma osmolality. (From Robertson GL. Thirst and vasopressin function in normal and disordered states of water balance. *J Lab Clin Med.* 1983;101:351–371, with permission.)

Stimuli to Arginine Vasopressin Secretion in Patients with SIADH

Regardless of the pattern of pituitary AVP secretion, and whether this represents an "inappropriate" or physiologically "appropriate" secretion, it is important to try to identify the cause(s) of the continued AVP secretion in patients with this disorder. Because of the variety of stimuli that can stimulate AVP secretion independent of osmolality, it seems logical to hypothesize that SIADH can be caused by continued nonosmotic stimulation of AVP secretion despite the presence of plasma hypoosmolality. The effect of hypovolemia to lower the threshold and increase the sensitivity of osmotically stimulated AVP secretion is well known, and this mechanism almost certainly accounts for the elevated plasma AVP levels in patients with edema-forming disorders in whom a decreased EABV activates baroreceptor-mediated AVP secretion.[42,43] Tumor interference with vagal pathways to brainstem baroreceptive centers could conceivably mimic

or exaggerate such hypovolemic conditions, potentially accounting for the occurrence of a reset osmostat pattern of AVP secretion found in some patients with cancers. Recent reports of a 3% to 4% incidence of SIADH in patients with advanced head and neck malignancies represents a group in which some, although clearly not all,[203] of the hyponatremia might also be secondary to interference with vagal baroreceptor pathways.[204] However, not all cases of SIADH can be comfortably ascribed to nonosmotic stimuli because it is difficult to identify any such possible stimuli in many patients. Another possibility is that brain pathways conveying afferent signals that actively inhibit AVP secretion from hypothalamic magnocellular neurons may be impaired in some patients. Substantial data support the likelihood that hypoosmolality does not simply lead to decreased AVP secretion by virtue of absence of excitatory osmoreceptor inputs, but rather represents a state of active inhibition of the AVP-secreting neurons,[205] possibly via endogenous opioid[206] or gamma-amino butyric acid (GABA) pathways.[109,207] In this case, it would be easy to imagine that impairments or alterations in the activity of these inhibitory pathways might allow continued AVP secretion despite hypoosmolality. Although such abnormalities have not yet been identified, there is one clinical situation in which a decreased inhibitory tone to AVP neurons does clearly lead to enhanced AVP secretion: elderly patients have decreased AVP responses to orthostasis but exaggerated responses to osmotic stimuli.[208,209] The latter is presumably due to a diminution of inhibitory, as well as excitatory, inputs from brainstem baroreceptive centers to the hypothalamus, thereby producing an unopposed stimulation by osmotic stimuli from the anterior hypothalamus (Fig. 70.4). This phenomenon could contribute to the unusually high frequency of SIADH seen in elderly individuals.[7,13,14,163,164] Despite our lack of precise information about the mechanisms responsible for osmotically inappropriate AVP secretion, it seems certain that this will prove to be a heterogeneous group of processes rather a single dominant cause.[210]

Contribution of Natriuresis to the Hyponatremia of SIADH

Because of the original cases studied by Schwartz and Bartter, increased renal Na^+ excretion has been viewed as one of the cardinal manifestations of SIADH, indeed one which later became embedded in the requirements for its diagnosis.[2] However, next to the use of the term "inappropriate," probably no other aspect of SIADH has been so widely misinterpreted. Demonstration that the natriuresis accompanying administration of antidiuretic hormone is not due to AVP itself but rather to the volume expansion produced as a result of water retention was unequivocally shown by Leaf even before the description of the clinical occurrence of this disorder.[46] Subsequent metabolic balance studies demonstrated that excess urinary Na^+ excretion and a negative Na^+ balance occurred during the development of hyponatremia in patients with SIADH, but eventually urinary sodium excretion simply reflected daily sodium intake.[1] Patients appear to exhibit renal sodium wasting because they continue to excrete sodium despite being hyponatremic, but in reality they have simply achieved a new steady-state in which they are in neutral sodium balance, albeit at a lower serum [Na^+]. Although this interpretation is now supported by abundant clinical and experimental evidence, several important questions remain unanswered regarding natriuresis and hyponatremia: What physiologic and/or pathophysiologic mechanisms underlie the natriuresis? Is natriuresis in SIADH always secondary to AVP-induced water retention or is hyponatremia sometimes caused primarily by Na^+ losses? Even when natriuresis is secondary to water retention, can the natriuresis further aggravate the hyponatremia?

As described previously, studies of long-term antidiuretic-induced hyponatremia in both dogs and rats have indicated that a larger proportion of the hyponatremia is attributable to secondary Na^+ losses rather than to water retention.[75,76] However, it is important to appreciate that in these models the natriuresis actually did not worsen the hyponatremia, but rather allowed volume regulation of blood and ECF volumes to occur. Therefore, over long periods, what begins as a "purely" dilutional hyponatremia from water retention becomes a mixed hyponatremia in which urinary solute losses allow maintenance of equivalent levels of hyponatremia but with lesser degrees of volume expansion due to water retention. Much of the past difficulty in consistently demonstrating expanded plasma or ECF volumes in patients with SIADH using tracer dilution techniques[77–79] can probably be ascribed to this process. It has become clear that intrinsic renal mechanisms are capable of producing both diuresis and natriuresis in response to increases in renal perfusion pressures; this mechanism has been shown to underlie the renal escape from antidiuresis produced when AVP-infused animals are continually fluid loaded.[48] However, it has not yet been proved whether this mechanism is sufficiently sensitive to detect the relatively mild degrees of volume expansion that accompany dilutional hyponatremias. Another, not mutually exclusive, possibility is that the natriuresis is mediated via increases in circulating natriuretic peptides such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Most cases of SIADH have been shown to have elevated levels of these peptides into ranges that are capable of promoting renal sodium excretion.[49,50,211] The degree to which hyponatremia occurs primarily as a result of natriuresis has remained controversial over many years. Cerebral salt wasting (CSW) was first proposed by Peters in 1950[212] as an explanation for the natriuresis and hyponatremia that sometimes accompanies intracranial disease, particularly subarachnoid hemorrhage (SAH), in which up to one third of patients often develop hyponatremia. Following the first clinical description of SIADH in 1957, such patients were generally assumed to have hyponatremia secondary to AVP hypersecretion with a secondary natriuresis.[213] However, over the last decade, clinical and experimental data have

suggested that some patients with SAH and other intracranial diseases may actually have a primary natriuresis leading to volume contraction rather than SIADH,[214–217] in which case the elevated measured plasma AVP levels may actually be physiologically appropriate for the degree of volume contraction present. The major clinical question as to the frequency of CSW as a cause of hyponatremia is dependent on the criteria used to assess the ECF volume status of these patients; opponents argue that there is insufficient evidence of true hypovolemia despite ongoing natriuresis,[218] whereas proponents argue that the combined measures that have traditionally been used to estimate ECF volume do in fact support the presence of hypovolemia in many cases.[219,220] With regard to the potential mechanisms underlying the natriuresis, both plasma and cerebrospinal fluid (CSF) ANP and BNP levels are clearly elevated in many patients with SAH,[217,221–223] and have been found to correlate variably with hyponatremia in patients with intracranial diseases.[217,223,224] However, because SIADH also is frequently associated with elevated plasma ANP and BNP levels, this finding alone does not prove causality. Ample precedent certainly exists for hyponatremia due to sodium wasting with secondary antidiuresis in Addison's disease, as well as diuretic-induced hyponatremia. Characteristic of these disorders, normalization of ECF volume with isotonic NaCl infusions restores plasma tonicity to normal ranges by virtue of shutting off secondary AVP secretion. If hyponatremia in patients with SAH occurred via a similar mechanism, it should also respond to this therapy. However, studies indicate that it does not. Nineteen patients with SAH were treated with large volumes of isotonic saline sufficient to maintain plasma volume at normal or slightly elevated levels, but despite removal of any volume stimulus to AVP secretion, 32% still developed hyponatremia in association with nonsuppressed plasma AVP levels, an incidence equivalent to that found in previous studies of SAH.[225] In contrast, other studies have demonstrated that mineralocorticoid therapy to inhibit natriuresis can reduce the incidence of hyponatremia in patients with subarachnoid hemorrhage[226]; such results are not unique to patients with intracranial diseases because a subset of elderly patients with SIADH have also been shown to respond favorably to mineralocorticoid therapy.[227] Although seemingly disparate, these types of results support the existence of disordered AVP secretion as well as a coexisting stimulus to natriuresis in many such patients. It seems most likely that SAH and other intracranial diseases represent a mixed disorder in which some patients have both exaggerated natriuresis and inappropriate AVP secretion; which effect predominates in terms of the clinical presentation will depend on their relative intensities as well as the effects of concomitant therapy. The possibility of ANP- or BNP-induced natriuresis aggravating hyponatremia is not confined to intracranial diseases, and it has been suggested that ectopic ANP production might contribute to, or even cause, the hyponatremia accompanying some small cell lung cancers.[228] In support of this, several studies have analyzed tumor cell lines from patients with hyponatremia and small cell lung carcinoma and found that many produced ANP or ANP mRNA in addition to, or in some cases instead of, AVP.[229–231] These data allow the possibility that some patients with tumors may also develop hyponatremia as a result of ectopic ANP secretion. However, in clinical studies of such patients, the hyponatremia appears to correlate more with the plasma AVP levels than the plasma ANP levels.[232] Consequently, it seems likely that such cases represent a mixture of inappropriate secretion of both hormones, analogous to patients with cerebral salt wasting, in which case the ANP and BNP could act to further exacerbate the secondary natriuresis produced primarily by AVP-induced water retention.

ADRENAL INSUFFICIENCY

The frequent occurrence of hyponatremia in patients with adrenal insufficiency was appreciated well before the discovery of the role of AVP in hypoosmolar disorders.[233] Incidences as high as 88% have been reported in patients with primary adrenal insufficiency, particularly during episodes of addisonian crisis.[234,235] This section summarizes the factors related to the development of hyponatremia in patients with adrenal insufficiency.

Etiology

The adrenal cortex produces many different types of corticosteroids, which can be broadly divided into three categories: glucocorticoids, mineralocorticoids, and androgens. Only the first two of these have been found to have significant effects on body fluid homeostasis. Disorders of impaired adrenal function can be divided into those in which the adrenal gland itself is damaged or destroyed, or primary adrenal insufficiency, and those in which the adrenal gland does not receive appropriate adrenocorticotropic hormone (ACTH) stimulation from the pituitary, or secondary adrenal insufficiency. Addison disease is the major cause of primary adrenal insufficiency and hypopituitarism is the best example of secondary adrenal insufficiency. The clinical presentation of these two types of adrenocortical insufficiency varies significantly, because adrenal destruction causes loss of both mineralocorticoids and glucocorticoids, whereas pituitary insufficiency causes only glucocorticoid insufficiency. This is because pituitary ACTH is not necessary for mineralocorticoid secretion, which is controlled primarily via the renin-angiotensin system. To understand the fluid and electrolyte abnormalities that accompany these disorders, the pathophysiology of hyponatremia due to mineralocorticoid and glucocorticoid deficiency must be considered separately.

Pathophysiology

Mineralocorticoid Deficiency

The absence of aldosterone impairs Na^+-K^+ exchange in the distal tubule. Because this defect occurs distally in the nephron, it cannot be completely compensated for by later Na^+

reabsorption, leading to the continued renal Na^+ excretion, or "salt wasting," that is the hallmark of primary adrenal insufficiency.[236] As long as sodium intake is sufficient to replace the ongoing renal losses, patients with mineralocorticoid insufficiency remain relatively stable. However, when sodium intakes are not sufficient, adrenally insufficient patients develop progressive hypovolemia, hyponatremia, and hyperkalemia, the classic fluid and electrolyte manifestations of addisonian crisis.[234,235] Proof that these effects were indeed caused primarily by the renal Na^+ losses was documented long ago by studies in animals[236,237] and addisonian patients,[238] which demonstrated that all of these abnormalities could be prevented by volume repletion with NaCl. However, the water retention of mineralocorticoid deficiency has multiple potential causes: (1) loss of aldosterone-mediated Na^+ reabsorption in the distal tubule impairs urinary dilution, similar to the use of thiazide diuretics; (2) ECF volume contraction as a result of the Na^+ losses causes increased fluid reabsorption in the proximal tubule with decreased delivery to the distal diluting segments of the nephron; and (3) ECF volume contraction also stimulates baroreceptor-mediated (i.e., nonosmotic) AVP secretion with resultant antidiuresis.

Numerous experimental studies have documented elevated plasma AVP levels despite hypoosmolality in adrenalectomized animals with mineralocorticoid insufficiency,[239–241] and the elevated AVP levels generally return to normal ranges following volume replacement with NaCl.[239] Proof that the elevations in plasma AVP levels were causally related to the water retention was provided by studies in which adrenalectomized rats replaced with only glucocorticoids were given a vasopressin V_2 receptor antagonist[242]; the antagonist significantly reduced urine osmolality in chronically, but not acutely, mineralocorticoid-deficient rats, consistent with hypovolemia-mediated stimulation of AVP secretion as a result of progressive Na^+ depletion over time. Conversely, AVP-independent effects appear to play some role in the water retention as well. Studies in adrenalectomized homozygous Brattleboro rats, which cannot synthesize AVP, have demonstrated normalization of urine dilution, free water clearance, and solute clearance following physiologic aldosterone, but not glucocorticoid, replacement.[243] These results demonstrate the contribution of multiple factors such as impaired urinary dilution due to the loss of aldosterone-mediated Na^+ reabsorption in the distal tubule, and increased proximal tubular fluid reabsorption as a result of hypovolemia, to the impaired water excretion of mineralocorticoid deficiency. The latter factor would be predicted to be reversed by volume repletion but not the former, possibly accounting for the observation that in some studies human patients with primary adrenal insufficiency still maintained higher urine osmolalities even under conditions of volume expansion,[244] although other studies in humans[238] and animals[245] have shown complete normalization of water excretion following volume expansion. Whatever the contribution of these additional factors, it nonetheless seems appropriate to conclude that the major mechanism responsible for the impaired water excretion of mineralocorticoid deficiency is hypovolemia-stimulated AVP secretion.

Glucocorticoid Deficiency

As described previously, isolated glucocorticoid deficiency generally occurs with pituitary disorders that impair normal ACTH secretion but leave other stimuli to aldosterone secretion intact. That glucocorticoid deficiency alone could also impair water excretion was recognized based on longstanding clinical observations that anterior pituitary insufficiency ameliorates, and sometimes even completely masks, the polyuria of patients with coexistent central diabetes insipidus.[246] It is not surprising, therefore, that hyponatremia occurs relatively frequently in hypopituitary patients without diabetes insipidus.[91,247,248] However, hypopituitary patients generally do not develop ECF volume contraction because they maintain adequate aldosterone secretion to prevent renal sodium wasting. Consequently, volume replacement with NaCl does not reverse the impaired water excretion of patients with secondary adrenal insufficiency as it does in primary adrenal insufficiency.[244]

Despite the lack of an apparent hypovolemia-mediated stimulus to AVP secretion, nonetheless nonosmotic AVP secretion has been strongly implicated in the impaired water excretion of glucocorticoid insufficiency. Elevated plasma AVP levels have clearly been documented in animals[249] and patients[101] with hypopituitarism (Fig. 70.6). Similarly, because primary adrenal insufficiency has components of both mineralocorticoid and glucocorticoid deficiency, adrenalectomized animals maintained only on physiologic replacement doses of mineralocorticoids also have been found to have inappropriately elevated plasma AVP levels.[250,251] That these elevated AVP levels were causally related to the impaired water excretion was again proved by studies using an AVP V_2 receptor antagonist, which demonstrated near normalization of urinary dilution in adrenalectomized mineralocorticoid-replaced rats.[242] However, as with mineralocorticoid deficiency, AVP-independent mechanisms have also been suggested to play a role in the impaired water excretion of glucocorticoid deficiency because Brattleboro rats maintained on aldosterone had somewhat decreased urine flow which increased following glucocorticoid replacement.[243] Because ECF volume depletion is generally not a manifestation of glucocorticoid deficiency, other factors must therefore be responsible for the AVP-independent aspects of the water retention. The possibility that glucocorticoids exerted direct effects on renal tubular epithelium, such that glucocorticoid insufficiency causes increased water permeability in the collecting tubules, even in the absence of AVP, has been suggested.[244] However, studies on isolated collecting tubules have failed to demonstrate any significant influence of glucocorticoids on water permeability of this tissue.[252] Consequently, the AVP-independent effects of

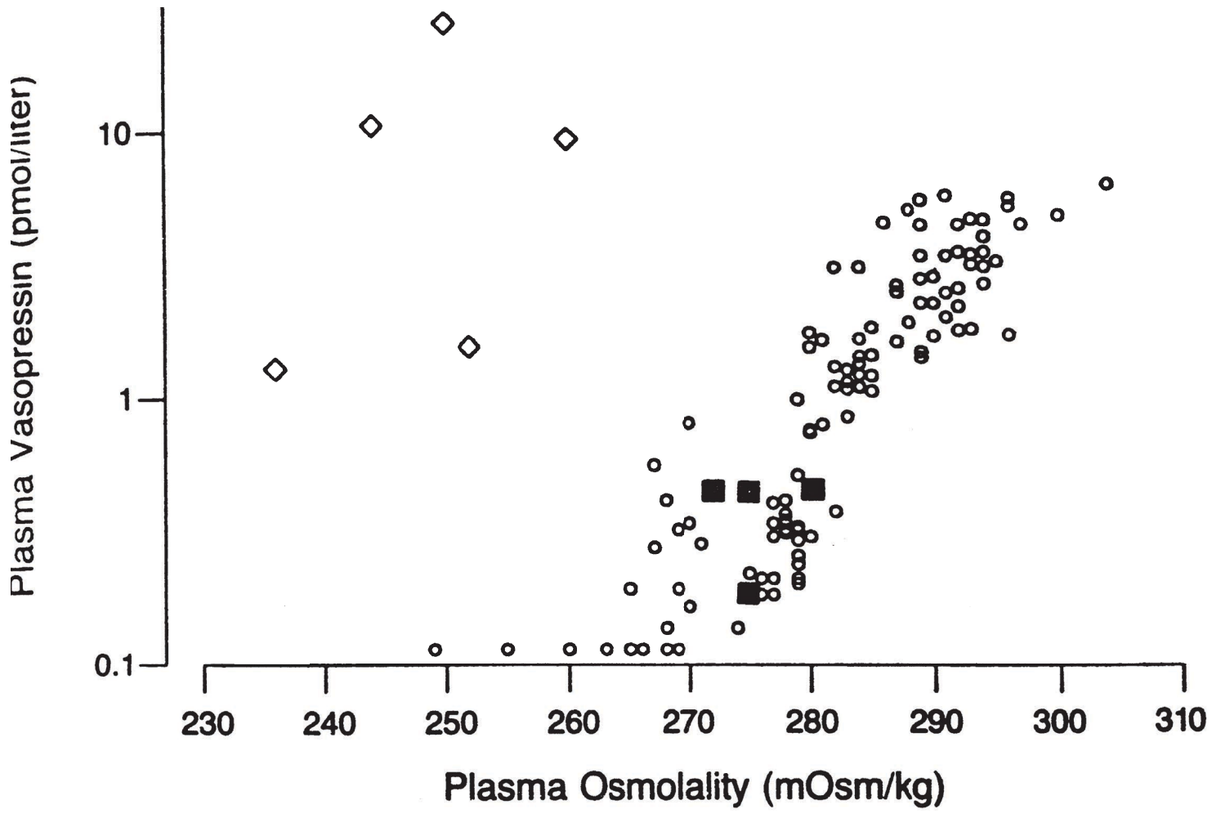

FIGURE 70.6 Plasma AVP levels as a function of plasma osmolality in patients with hypopituitarism and ACTH insufficiency. The *diamonds* show patients with untreated hypopituitarism and the *solid squares* the same patients after hydrocortisone therapy. The *open circles* depict AVP levels in normal subjects over physiologic ranges of plasma osmolality. In comparison with Figure 70.3, it is apparent that these patients would be indistinguishable from those with SIADH based on their plasma AVP-osmolality relation. (From Oelkers W. Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Eng J Med.* 1989;321:492–496, with permission.)

glucocorticoid insufficiency remain poorly defined at the present time.

Regardless of the etiology of the AVP-independent defect in water excretion, the major mechanism responsible for the impaired water excretion of glucocorticoid deficiency appears to be nonosmotically stimulated AVP secretion. However, the stimulus to AVP secretion under these conditions also remains unclear. Studies of prolonged glucocorticoid insufficiency in dogs have shown an increased pulse pressure and decreased cardiac stroke volume,[250] and similar studies in rats have suggested decreases in cardiac index along with increased systemic vascular resistance.[251] Although these findings differ somewhat, in both cases they raise the possibility of hemodynamically mediated effects on AVP secretion. Alternatively, glucocorticoid deficiency might directly stimulate AVP secretion via two possible mechanisms. First, both clinical[253] and experimental[254] studies have shown a modest but significant effect of glucocorticoids to inhibit pituitary AVP secretion. Presumably this is mediated via glucocorticoid receptors that have been localized in magnocellular neurons[255]; interestingly, recent studies have shown that these receptors are increased during induced hypoosmolality, suggesting that glucocorticoids may play a role in the inhibition of AVP secretion under hypoosmolar conditions.[256] Second, in the absence of glucocorticoid feedback inhibition of the parvocellular AVP neurons that project to the median eminence rather than to the posterior pituitary, AVP content increases markedly in this area.[257,258] This presumably reflects increased secretion of AVP into the pituitary portal blood system in order to stimulate pituitary ACTH secretion.[259–262] Because the pituitary portal blood eventually drains into the systemic circulation, increased levels of AVP released from the median eminence could therefore increase plasma AVP levels sufficiently to produce some degree of inappropriate antidiuresis; it is important to remember that such levels need not be very high, but simply inappropriate for the plasma osmolality, as shown in Figures 70.3 and 70.6.

HYPOTHYROIDISM

Although hypothyroidism is considerably more common than adrenal insufficiency, hyponatremia secondary to hypothyroidism occurs much less frequently than hyponatremia from adrenal insufficiency. The infrequent occurrence of hyponatremia with hypothyroidism has led some to question whether hypothyroidism is in fact causally related to hyponatremia,[263] but this is likely a manifestation of the fact that impaired water excretion is only seen in more severely hypothyroid patients. Typically such patients are elderly and meet criteria for myxedema coma as a result of their altered mental status.[264,265] This section summarizes the factors related to the development of hyponatremia in patients with hypothyroidism.

Etiology

Similar to adrenal insufficiency, hypothyroidism can result from either dysfunction or damage to the thyroid gland itself, or primary hypothyroidism, or from inadequate thyroid-stimulating hormone (TSH) stimulation from the pituitary, or secondary hypothyroidism. Also similar to adrenal insufficiency, there can be significant differences in the presentation of these two disorders. However, because the only biologically active products of the thyroid gland are the hormones thyroxine (T_4) and triiodothyronine (T_3), in this case the clinical variations are due mainly to quantitative differences in the severity of the thyroid hormone deficiency rather than to qualitative differences in the nature of the hormone deficits. With moderate degrees of hypothyroidism, patients with both primary and secondary disease have similar signs and symptoms of thyroid hormone deficiency (e.g., cold intolerance, increased fatigue, dry skin, constipation, etc.), but generally only patients with primary hypothyroidism progress to more severe degrees of myxedema, including the life-threatening metabolic and neurologic abnormalities of myxedema coma. These extreme manifestations are virtually never seen with secondary hypothyroidism. This is because

severe myxedema occurs only after plasma T_4 and T_3 levels have fallen to very low levels, often <1 μg per dL. This scenario can easily occur with primary hypothyroidism since in the absence of thyroid tissue there is no alternative source of thyroid hormone production. However, T_4 and T_3 levels never decrease as severely in hypopituitary patients who simply lack TSH, and frequently plasma levels remain just at or slightly below the lower limits of normal.[266] This likely reflects either some degree of constitutive thyroid hormone synthesis by the thyroid gland, or possibly low grade stimulation of TSH receptors by other circulating substances, analogous to the thyrotoxicosis produced by thyroid stimulating immunoglobulins in patients with Graves disease. Because hyponatremia is seen only in hypothyroid patients who have progressed to severe degrees of myxedema, it follows that this manifestation generally occurs in patients with primary hypothyroidism. When hyponatremia accompanies hypopituitarism it is usually a manifestation of secondary adrenal insufficiency from glucocorticoid deficiency rather than the coexisting hypothyroidism.[90,267]

Pathophysiology

Several studies have clearly confirmed abnormalities of water excretion in hypothyroid patients. However, in almost all cases, the abnormality was found to consist of a delayed excretion of water rather than major impairments in urinary dilution.[268–270] This was best shown in the studies of DeRubertis et al., in which near normal urinary dilution occurred following water loading in hypothyroid patients (Fig. 70.7), even though cumulative excretion of the water load in the hypothyroid patients lagged far behind that of euthyroid controls (39.8 ± 5.1% versus 78.7 ± 5.7%) after 2 hours.[269] Similar results have been found in studies of hypothyroid rats.[271,272] Experimental studies in hypothyroid animals have implicated decreases in renal blood flow and GFR as the primary factors responsible for the delayed water excretion. In particular, the relation between free water clearance and distal tubular Na^+ delivery was found to be identical in hypothyroid and euthyroid rats, suggesting that the observed impairments in water excretion were likely secondary to reduced delivery of glomerular filtrate to the distal nephron in the hypothyroid rats.[271] These results are consistent with findings of a decreased GFR in severely hypothyroid patients,[269,273,274] which is most likely due to decreased renal blood flow as a result of the compromised cardiac output and increased peripheral vascular resistance known to occur in severely hypothyroid patients.[275–277] Experimental studies have also supported this hypothesis because a variety of maneuvers that increase distal tubular fluid delivery (e.g., carbonic hydrase inhibition, isotonic saline infusion, and unilateral nephrectomy) all markedly increase free water clearance in hypothyroid rats.[271,278,279] Therefore, similar to patients with edema-forming states, hypothyroid patients have increased proximal Na^+ and water absorption as a result of decreased EABV with subsequent decreased delivery of tubular fluid to the distal diluting sites of the nephron, thereby accounting for much of their impaired rate of water excretion.

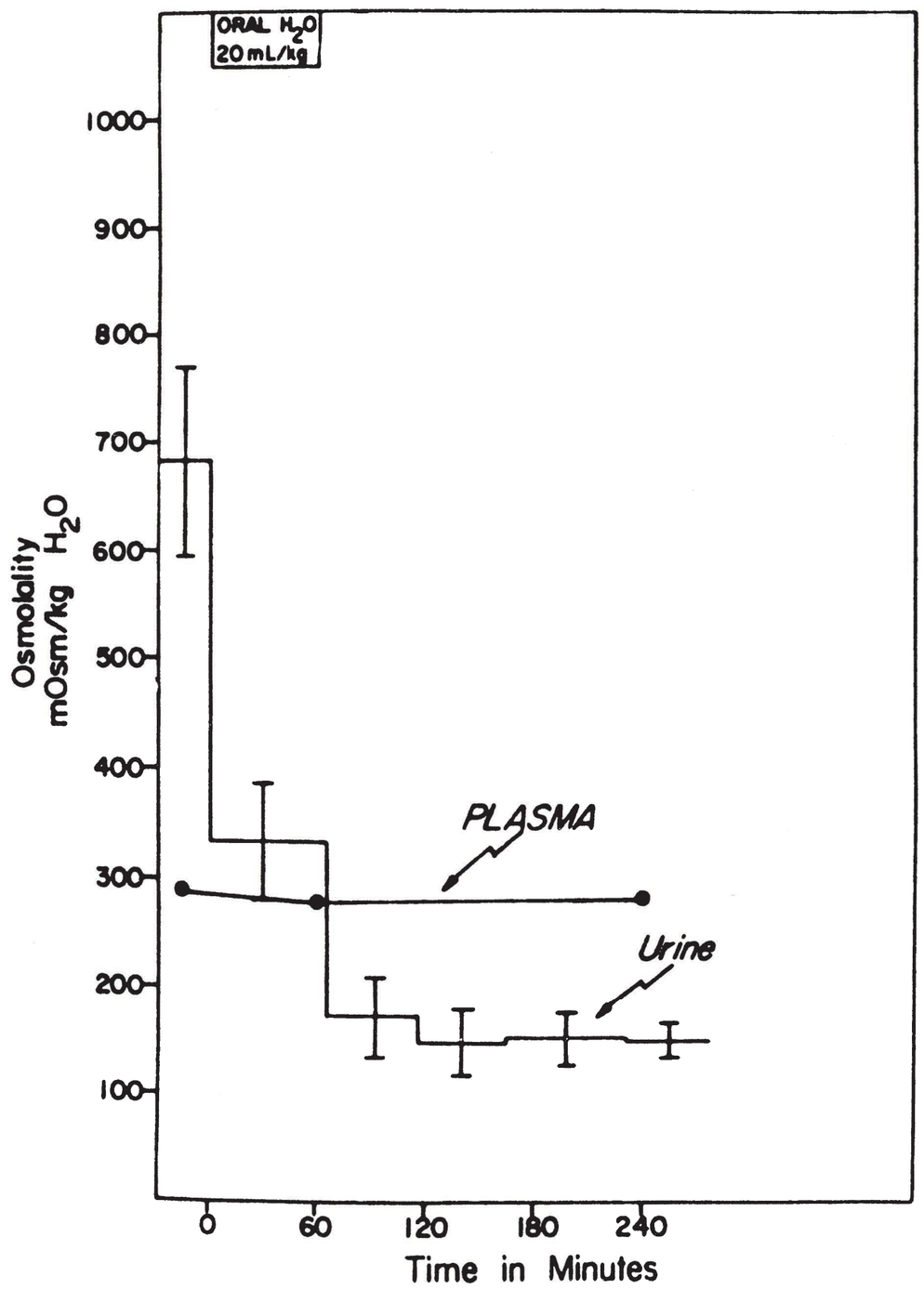

FIGURE 70.7 Mean plasma and urine osmolalities in 16 patients with untreated myxedema for 6 hours following an oral water load (20 mL per kg body weight). Urine osmolalities decreased significantly to <200 mOsm per kg H_2O by 4 hours after the water load, indicating fairly intact renal diluting mechanisms in these patients. (From Derubertis FR Jr, Michelis MF, Bloom ME, et al. Impaired water excretion in myxedema. *Am J Med.* 1971;51:41–53, with permission.)

As noted previously, patients with edema-forming states also have baroreceptor-mediated stimulation of AVP secretion that leads to further impairment of free water excretion by preventing maximal urinary dilution.[194] The results of some studies have supported a similar dual effect in hypothyroid patients as well. Fifteen of 20 patients studied by Skowsky and Kikuchi had elevated plasma AVP levels even after water loading, which then suppressed normally after the patients were made euthyroid.[270] Similarly, other investigators have found frankly elevated plasma AVP levels,[280,281] inappropriately normal levels despite plasma hypoosmolality,[281] or a decreased osmotic threshold for AVP secretion in hypothyroid patients.[282] Conversely, equal numbers of studies have failed to find evidence of inappropriately elevated plasma AVP levels, urine AVP secretion, or significantly altered osmotic thresholds for AVP secretion or urinary dilution in hypothyroid patients.[269,283–285] Consistent with these findings are several reported cases in which treatment with

demeclocycline to antagonize renal AVP effects failed to increase serum [Na^+] or decrease urine osmolality in hyponatremic hypothyroid patients.[283,286] Experimental studies have also shown variable results. Hypothyroid rats have been reported to manifest higher plasma AVP levels than euthyroid rats after water loading.[272] However, hypothyroid Brattleboro rats appear to have similar defects in water excretion as rats with intact AVP secretion,[271] supporting a major role for AVP-independent mechanisms of impaired free water excretion in hypothyroid animals. Recent studies of hypothalamic AVP gene expression have failed to demonstrate upregulation of AVP synthesis in hypothyroid rats,[287] again arguing against a major stimulation of AVP secretion under these conditions, although the sensitivity of these methods for ascertaining small increases in hormone secretion and synthesis is limited. Perhaps the strongest argument against a major role for AVP-stimulated water retention in hypothyroidism has been the failure of any animal model of hypothyroidism to date to reproduce the degrees of hyponatremia commonly found in animal models of SIADH, adrenal insufficiency, and cardiac failure.

In light of the clinical and experimental observations to date, it has to be concluded that the major cause of impaired water excretion in hypothyroidism is an alteration in renal perfusion and GFR secondary to systemic effects of thyroid hormone deficiency on cardiac output and peripheral vascular resistance. Yet it must be recognized that severe hypothyroidism is a multisystem disease—just as the presentation of patients with SIADH will vary depending on the degree of volume adaptation that has occurred, it is hardly surprising that different results have been reported regarding the potential role of AVP in hypothyroidism depending on the individual characteristics of the cases studied. Therefore, in uncomplicated hypothyroidism there appears to be little elevation of plasma AVP levels, and any defects in water excretion are due primarily to effects on renal hemodynamics. As the hypothyroidism becomes more severe, EABV can decease sufficiently to stimulate AVP secretion secondarily via baroreceptor mechanisms. However, even in this case the elevated AVP levels may not be causally related to the impaired water excretion because several studies have suggested that hypothyroid animals are resistant to the effects of AVP based on decreased medullary cyclic AMP generation in response to AVP.[272,288] However, when cardiac function becomes severely compromised, as can occur with advanced myxedema, plasma AVP can become elevated sufficiently to override any renal resistance and cause an antidiuresis, which then contributes to the hemodynamic impairments of water excretion. Whether hyponatremia develops at any stage of disease progression depends on the relative balance between water intake and excretory capacity. Because maximal free water clearance decreases as these defects become more pronounced, this accounts for the increased incidence of hyponatremia as the severity of the underlying hypothyroidism worsens.

PRIMARY POLYDIPSIA

As discussed previously, excessive water intake is only rarely of sufficient magnitude to produce hyponatremia in the presence of normal renal function. However, it is often a significant factor contributing to hyponatremia in polydipsic patients, particularly those with underlying defects in free water excretion. In addition, because a positive water balance is required for the production of hyponatremia even under conditions of maximal antidiuresis in man and animals, an appreciation of the control mechanisms regulating water ingestion is important for understanding the development of hyponatremia in patients with SIADH and other hypoosmolar disorders.

Etiology

The most dramatic cases of primary polydipsia are seen in psychiatric patients, particularly in those with acute psychosis secondary to schizophrenia.[289–293] The prevalence of this disorder based on hospital admissions for acute symptomatic hyponatremia may have been underestimated, since studies of polydipsic psychiatric patients have shown a marked diurnal variation in serum [Na^+] (from 141 mEq per L at 7 AM to 130 mEq per L at 4 PM), suggesting that many such patients drink excessively during the daytime but then correct themselves via a water diuresis at night.[294] This and other considerations have led to defining this disorder as the psychosis-intermittent hyponatremia-polydipsia (PIP) syndrome. Polydipsia has been observed in up to 20% of psychiatric inpatients,[293] with incidences of intermittent hyponatremia ranging from 5% to 10%.[293,295,296] Despite the frequent occurrence of polydipsia in psychiatric patients, it is important to recognize that not all polydipsia is caused by psychiatric disease; infiltrative diseases such as CNS sarcoidosis[297] or critically placed brain tumors can also be associated with increased thirst and fluid ingestion. Consequently, polydipsic patients should be evaluated with a CT or MRI scan of the brain before concluding that excessive water intake is due to a psychiatric cause.

Pathophysiology

There is little question that excessive water intake alone can sometimes be sufficient to override renal excretory capacity and produce severe hyponatremia.[40,298] Although the water excretion rate of normal adult kidneys can exceed 20 L per day, maximum hourly rates rarely exceed 800 to 1,000 mL per hour. Recent studies of water loading in exercising athletes have indicated a similar peak urine excretion rate of 778 ± 39 mL per hour.[299] Because many psychiatric patients drink predominantly during the day or during intense drinking binges,[291,294,300,301] they can transiently achieve symptomatic levels of hyponatremia with total daily volumes of water intake less than 20 L if it is ingested sufficiently rapidly. This likely accounts for many of the cases in which such patients present with maximally dilute urine, accounting for as many as 50% of patients in some studies,[302] and correct quickly via a free water diuresis.[303] However, other cases

have been found to meet the criteria for SIADH,[292,302,304–306] suggesting nonosmotically stimulated AVP secretion. As might be expected, in the face of much higher than normal water intakes, virtually any impairment of urinary dilution and water excretion can exacerbate the development of a positive water balance and thereby produce hypoosmolality. Hyponatremia has been reported in polydipsic patients taking thiazide diuretics[307,308] or drugs known to be associated with SIADH,[171,293,295,309–313] in association with smoking and presumed nicotine-stimulated AVP secretion[314–316] (although a consistent relation with smoking has not been found[172]), and adrenal insufficiency.[317] Acute psychosis itself can also cause AVP secretion,[290,318] which often appears to take the form of a reset osmostat.[189,291,305] It is therefore apparent that no single mechanism can completely explain the occurrence of hyponatremia in polydipsic psychiatric patients, but the combination of higher than normal water intakes plus even modest elevations of plasma AVP levels from a variety of potential sources appears to account for a significant portion of such cases.

Although patients with SIADH do not in general manifest the water intakes of patients with primary polydipsia, nonetheless continued water intake in the face of plasma hypoosmolality is inappropriate for maintenance of osmotic homeostasis. Analysis of daily fluid intakes of 91 hyponatremic patients showed an average fluid intake of 2.4 ± 0.2 L per 24 hours (Fig. 70.8),[41] which does not differ appreciably from earlier measured intakes of medical students or hospitalized cardiac patients (mean fluid intakes of 2.4 and 2.8 L per 24 hours, respectively[319]), or studies of middle-aged subjects (mean fluid intake of 2.1 L per 24 hours[320]). This consistent pattern of continued water intake in hyponatremic patients raises important questions as to its cause. Most, although not all, patients treated with dDAVP do not become hyponatremic because they limit their water intakes in the absence of stimulated thirst. This observation has suggested the possibility that patients with SIADH and other hypoosmolar disorders might have a coexisting defect in thirst regulation; recent studies have supported this possibility by showing a 20 mOsm per kg H_2O downward resetting of the thirst threshold in a group of patients with SIADH.[321] A potential underlying mechanism could be stimulation of thirst by central AVP hypersecretion, but to date only relatively small effects of AVP to stimulate thirst have been seen in a single species.[322] Alternatively, other animal studies have suggested that osmotic inhibition of thirst is a relatively weak phenomenon and easily overcome by a variety of nonhomeostatic stimuli causing drinking. Not only will rats increase intakes when fluids are made more palatable,[323] but rats made antidiuretic with dDAVP will continue to ingest such fluids to the point of extreme hypoosmolality and the degree of hypoosmolality achieved is proportional to the palatability of the fluid.[324] Analogous results have been obtained with schedule-induced polydipsia in rats treated with AVP.[325] In these examples drinking continued despite the production of both osmotic dilution and volume expansion, and despite drinking behavior sufficient to activate both oropharyngeal and gastrointestinal inhibitory factors that modulate fluid ingestion.[326] Obviously, drinking will not continue indefinitely in the absence of renal excretion until some factor causes inhibition of further intake, but before this happens it is possible to achieve plasma dilutions of 20% to 30%. In humans, similar to animals, there are many nonhomeostatic stimuli to drink fluids, including meal-associated drinking, oral habituation to various beverages, pleasurable sensations from palatable fluids, social interactions promoting fluid ingestion, and mouth dryness as a result of local factors, and these actually account for the major part of human fluid ingestion.[320] By themselves such stimuli are benign and simply lead to more frequent urination of dilute urine to excrete the increased fluids ingested. However, in the presence of pathologic conditions that impair renal water excretion they can lead to hyponatremia. Therefore, although direct inhibitory physiologic stimuli to thirst and fluid ingestion clearly exist, they appear to be relatively weak in comparison to excitatory stimuli and can be overridden by a variety of nonhomeostatic stimuli that cause continued fluid ingestion despite plasma hypoosmolality.[326] The extent to which such nonhomeostatic drinking versus disordered thirst regulation is responsible for the continued fluid ingestion in hypoosmolar disorders remains to be evaluated by more extensive clinical and experimental studies.

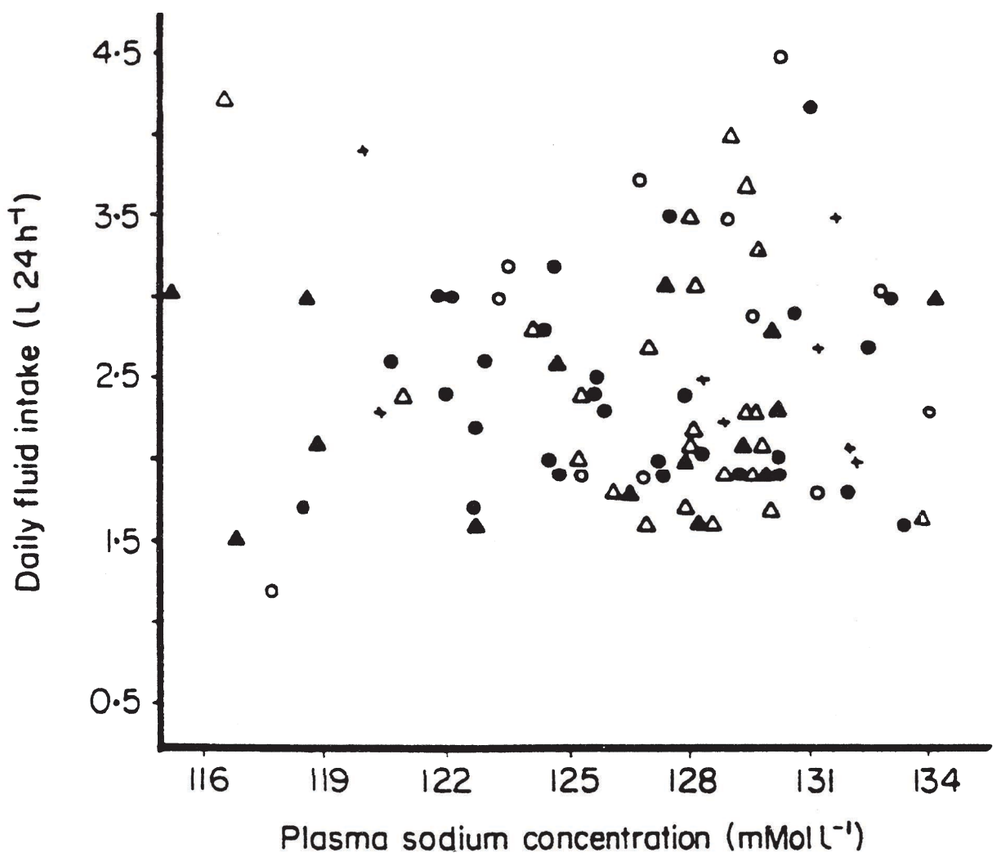

FIGURE 70.8 Daily fluid intakes of 91 hospitalized patients with hyponatremia of varying degrees and etiologies. Each point represents a single patient: *open circles*, SIADH; *open triangles*, cardiac failure; *closed circles*, volume contraction; *closed triangles*, cirrhosis; *pluses*, undiagnosed. Despite widely different etiologies for the hyponatremia, mean fluid intakes were equivalent in all groups of patients. (From Gross PA, Pehrisch H, Rascher W, et al. Pathogenesis of clinical hyponatremia: observations of vasopressin and fluid intake in 100 hyponatremic medical patients. *Eur J Clin Invest*. 1987;17:123–129, with permission.)

EXERCISE-ASSOCIATED HYPONATREMIA

Over the last three decades, exercise-associated hyponatremia (EAH) has emerged as an important complication of prolonged endurance physical activities. EAH is defined as the occurrence of hyponatremia in individuals engaged in prolonged physical activity who develop a serum or plasma [Na^+] below the normal reference range of the laboratory performing the test, generally less than 135 mEq per L.[327]

Etiology

The first cases of hyponatremia in association with prolonged physical activity were reported in 1985. Noakes et al. published a series of four case reports of athletes who developed hyponatremia (serum [Na^+] ranging from 115 to 125 mEq per L accompanied by fluctuating levels of consciousness, seizures, and pulmonary edema) during marathon footraces in South Africa.[150] Soon afterward, Hiller et al. reported that 27% of a prospectively studied cohort of the race finishers at the 1985 Hawaiian Ironman triathlon developed hyponatremia.[328] Since that time, well over 100 cases of EAH have been reported in the literature from physical exercise activities as diverse as forced military marches, prolonged hiking, and marathon, ultramarathon, and triathlon races, with several documented fatalities attributed to the hyponatremia.[329] Several prospective studies have been performed on subsets of runners participating in organized endurance activities and have documented incidences of hyponatremia from 13% to 29%.[151,330–332] Interestingly, for all studies in which sex differences have been examined, the incidence of hyponatremia has been found to be substantially higher in female athletes, ranging from 22% to 45%.[151,331,332] From the reported studies to date, it is clear that EAH can occur either during physical activity or within the 24-hour period after the activity, and most commonly occurs with prolonged physical activity generally lasting longer than 4 hours (although a few cases have been reported with physical activity of shorter durations[333]).

Pathophysiology

From the very first reports of EAH there has been a divergence of opinion regarding the underlying pathophysiology. Noakes has proposed that most cases of EAH represent a dilutional hyponatremia secondary to excess fluid ingestion during physical activity, similar to primary polydipsia,[156] whereas Hiller has implicated a depletional hyponatremia secondary to massive sodium losses from sweating during prolonged physical activity, especially in hot climates.[334] Multiple lines of evidence now strongly support the development of a dilutional hyponatremia from excess water retention as the primary cause of most of these cases. First, in virtually all studies where body weight has been recorded before and after exercise, there has been a consistent inverse relation between weight and serum [Na^+], indicative of fluid retention. This is best illustrated in the data from the New Zealand Ironman triathlon in 1997 (Fig. 70.9), in which the most severe hyponatremia occurred in athletes who actually gained weight during this event.[151] Second, high levels of fluid intake have been recorded in many of the athletes who develop EAH, often far in excess of the maximal renal excretory capacity of 800 to 1,000 mL per hour, and studies quantifying fluid intake have shown a significant negative correlation between ingested volumes and serum [Na^+].[331] Although fluid loses from sweating can be substantial during

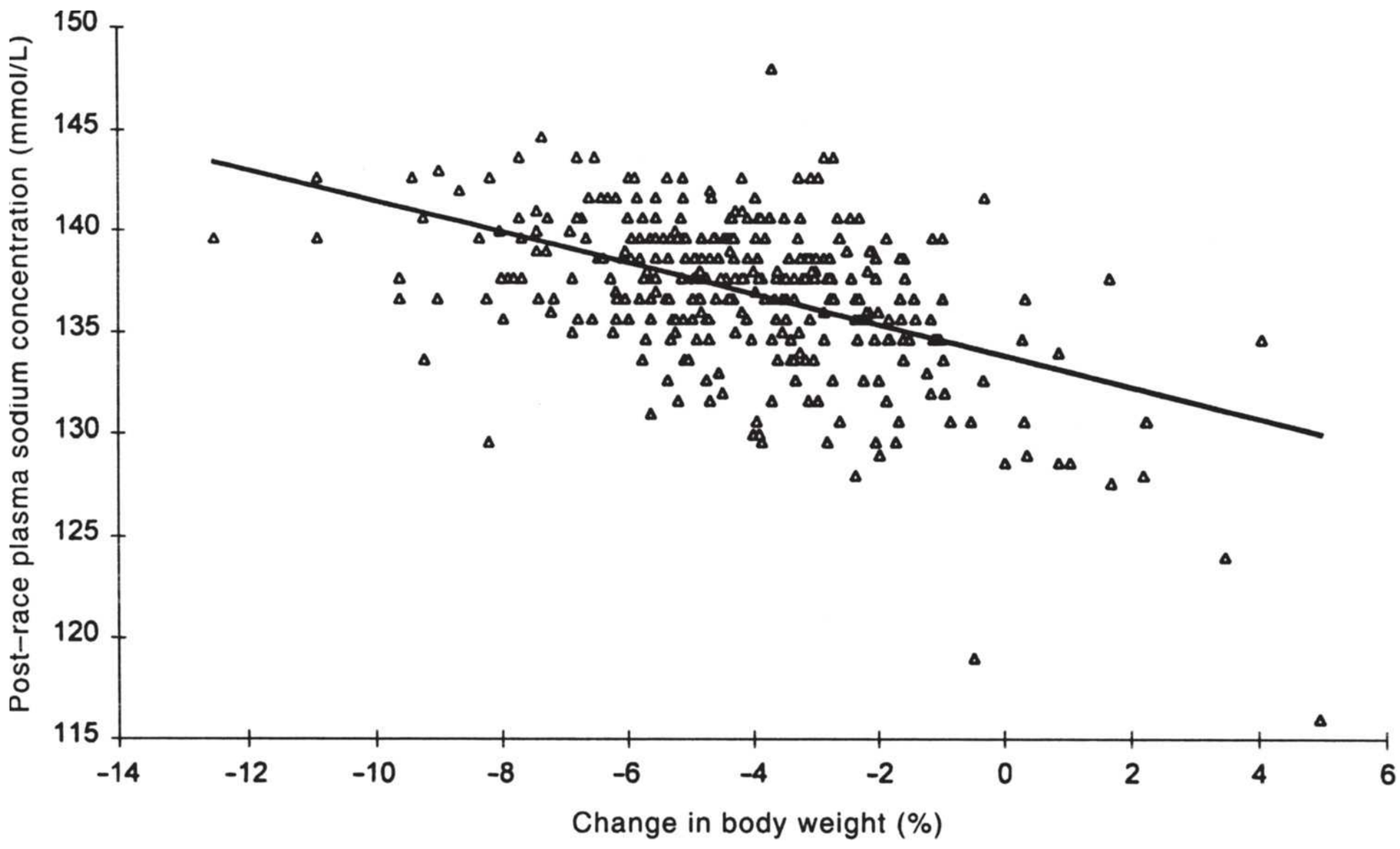

FIGURE 70.9 Inverse relation between the post-race plasma sodium concentrations in 350 athletes at the finish of the 1997 New Zealand Ironman triathlon as a function of changes in body weight during the race. (From Speedy DB, Noakes TD, Rogers IR, et al. Hyponatremia in ultradistance triathletes. *Med Sci Sports Exerc.* 1999;31(6):809–815, with permission.)

intense physical activity, this pattern of weight change suggests that fluid ingestion often exceeds the sum of fluid losses from renal excretion and sweating in EAH. Third, clinical evidence of volume depletion is not characteristic of most individuals who develop EAH (e.g., hyponatremic runners from the Houston marathon in 2000 manifested lower levels of BUN rather than developing a prerenal azotemia[331]). Fourth, two balance studies have been done on runners who developed EAH following ultramarathon races in comparison to a subset of normonatremic runners in these races.[335,336] Both of these studies showed that over a 9- to 24-hour period after the race, the hyponatremic runners corrected their serum [Na^+] via a free water diuresis of 1.3 to 3.0 L, indicating the development of water retention during the race, whereas the normonatremic runners retained 0.5 to 2.7 L, indicating the development of dehydration during the race. Both groups of runners had moderate positive sodium balances ranging from 88 to 153 mEq, indicating net sodium losses during the race, but the levels of sodium retention were not different between the hyponatremic and normonatremic runners.

Although the above data clearly implicate fluid retention as the major cause of EAH, additional data do not fully support the concept that this is solely due to excess drinking. A retrospective review of the U.S. Army inpatient data system from 1996–1997 revealed 17 cases of hyponatremia with a mean serum [Na^+] of 122 ± 5 mEq per L.[152] Virtually all of the cases occurred in the South during hot summer months, and most occurred in the first 4 weeks of military training. The majority presented with neurologic symptoms and had documented water intakes of greater than 2 quarts per hour. One recruit died from cerebral and pulmonary edema. Although these cases were all classified as due to overhydration on clinical grounds, detailed studies as to causation were not done. However, a more informative controlled study under similar conditions was performed earlier in Israel. Seventeen young males were studied during a 24-hour endurance march with ad libitum fluid ingestion. Serum [Na^+] levels decreased and were inversely related to total fluid intake, strongly suggesting a dilutional hyponatremia.[337] Despite the hyponatremia and a measured expanded plasma volume (+16%), maximal urine outputs were only 4 mL per minute with urine osmolalities of approximately 200 mOsm per kg H_2O, indicative of an inappropriate antidiuresis. Similarly instructive is a retrospective review of 44 hikers in the Grand Canyon who required medical treatment and had electrolytes measured in 1993.[153] Seven (16%) of the cases had hyponatremia, with serum [Na^+] ranging from 109 to 127 mEq per L; five of the seven had serious neurologic symptoms (three had seizures, two were disoriented) and had documented fluid intakes greater than the normonatremic patients (7.4 L versus 3.6 L), including sports drinks (4.3 L versus 0.5 L). Of particular significance, urine measurements showed osmolalities of 476 to 609 mOsm per kg H_2O and sodium levels of 36 to 120 mEq per L. A related study in Israel reported seven patients who developed hyponatremia (serum [Na^+] = 115 to 123) after moderate exercise with urine sodium levels of 74 to 122 mEq per L.[338] Most of these patients therefore met criteria for a diagnosis of SIADH, assuming the absence of thyroid and adrenal deficiencies, which are unlikely in young healthy individuals. Although SIADH had been dismissed in some reports because measured AVP levels were not "high," in this and other studies[158,159] it is clear that the plasma AVP levels were not suppressed in athletes with EAH, and consequently were inappropriate for their plasma osmolalities. It therefore seems very likely that EAH is caused by a combination of increased fluid intake in the setting of impaired renal excretory capacity during exercise. To what degree the decreased renal excretory capacity is secondary to renal hemodynamic changes, which can be marked during prolonged exercise, versus AVP-induced antidiuresis remains to be ascertained. Also unknown is the stimulus of AVP secretion during exercise. Although exercise itself is a mild stimulus of AVP secretion,[339] it is likely that hypovolemia from sweat sodium losses as well as nonhomeostatic stimuli (e.g., nausea, hypoglycemia, hypoxia, stress, increased cytokines from rhabdomyolysis) also are contributory.[158,159] The degree to which AVP secretion is stimulated, and whether it can be suppressed with sufficient fluid ingestion, will determine each individual's susceptibility to EAH as a result of fluid ingestion both before and after physical activity. Therefore, similar to the hyponatremia of schizophrenic patients, no single mechanism likely can completely explain the occurrence of hyponatremia in EAH, but the combination of higher than normal fluid intakes plus even modest elevations of plasma AVP levels from a variety of potential sources during prolonged physical activity appears to account for the majority of such cases.[340,341]

It is interesting to consider why EAH was not recognized prior to 1985. Noakes has drawn attention to the close temporal relationship between the recent reports of hyponatremia and changes in the conduct of endurance races.[156] First, these events became increasingly popular in the 1980s with large numbers of competitors, including competitors with lower fitness levels and hence longer running times. Second, multiple support stations to provide athletes with fluid at more frequent intervals during the race were introduced; prior to this time, fluid ingestion during prolonged exercise was considered unnecessary and possibly detrimental to performance. The convergence of these two developments is that athletes have more opportunity to drink during the events, and particularly the slower (i.e., novice) athletes. In support of this hypothesis, multiple studies have identified duration of time during races along with increased fluid consumption and weight gain as risk factors for the development of EAH.[331,332] Although female sex has also been frequently identified as a risk factor, a recent report from the 2002 Boston marathon has suggested that this variable might be explained by the lower body mass index (BMI) of female athletes, thus rendering them more susceptible to increased dilutional

effects of excess fluid retention because of a smaller total body water volume.[332]

CLINICAL MANIFESTATIONS OF HYPOOSMOLAR DISORDERS

Regardless of the etiology of hypoosmolality, the clinical manifestations are similar. Nonneurologic symptoms are relatively uncommon, but a number of cases of rhabdomyolysis have been reported,[342,343] presumably secondary to osmotically induced swelling of muscle fibers. Hypoosmolality is primarily associated with a broad spectrum of neurologic manifestations, ranging from mild nonspecific symptoms (e.g., headache, nausea) to more significant disorders (e.g., disorientation, confusion, obtundation, focal neurologic deficits, and seizures).[344–346] This neurologic symptom complex has been termed hyponatremic encephalopathy[347] and primarily reflects brain edema resulting from osmotic water shifts into the brain because of decreased effective plasma osmolality.[348] Significant neurologic symptoms generally do not occur until the serum [Na^+] falls below 125 mEq per L, and the severity of symptoms can be roughly correlated with the degree of hypoosmolality.[344,345] However, individual variability is marked, and for any single patient, the level of serum [Na^+] at which symptoms appear cannot be predicted with great accuracy. Much of this variability can be understood within the framework provided by the process of brain volume regulation (Fig. 70.1), as discussed previously.[71,72] Although most of the neurologic symptoms associated with acute hyponatremia are caused by brain edema as a result of osmotic water movement into the CNS, a potential exception is the development of seizure activity, which may possibly be caused or aggravated by increased brain ECF concentrations of the excitatory amino acids glutamate and aspartate as a result of cellular extrusion of these osmolytes during the process of brain volume regulation to hyponatremia.[68,349]

It is also well known from animal studies that the rate of fall of serum [Na^+] is often more strongly correlated with morbidity and mortality than is the actual magnitude of the decrease.[344] This is due to the fact that the volume-adaptation process takes a finite period of time to complete; the more rapid the fall in serum [Na^+], the more brain edema will be accumulated before the brain is able to lose solute and along with it part of the increased water content. These effects are responsible for the much higher incidence of neurologic symptoms, as well as the higher mortality rates, in patients with acute hyponatremia than in those with chronic hyponatremia.[344,350] This phenomenon also likely underlies the observation that the most dramatic cases of death due to hyponatremic encephalopathy have generally been reported in postoperative patients in whom hyponatremia often develops rapidly as a result of intravenous infusion of hypotonic fluids,[18,351] or in exercise-induced hyponatremia during endurance races or forced marches as a result of excess water ingestion.[152,352,353] In such cases, nausea and vomiting are frequently overlooked as potential early signs of increased intracranial pressure in acutely hypoosmolar patients. Because hypoosmolality does not cause known direct effects on the gastrointestinal tract, the presence of unexplained nausea or vomiting in a hypoosmolar patient should be assumed to be of CNS origin and the patient treated for symptomatic hypoosmolality as described in the subsequent text. A recent study of runners in a marathon race found that vomiting was the only symptom that differentiated hyponatremia from other causes of exercise-associated collapse in this group.[331] Similarly, critically ill patients with unexplained seizures should be rapidly evaluated for possible hyponatremia, since as many as one third of such patients have been found to have serum [Na^+] less than 125 mEq per L as a contributory cause of the seizure activity.[354]

Underlying neurologic disease also affects the level of hypoosmolality at which CNS symptoms appear; moderate hypoosmolality is generally of little concern in an otherwise healthy patient, but can cause morbidity in a patient with an underlying seizure disorder. Nonneurologic metabolic disorders (e.g., hypoxia,[355] acidosis, hypercalcemia) can similarly affect the level of plasma osmolality at which CNS symptoms occur.

In the most severe cases of hyponatremic encephalopathy, death results from respiratory failure after tentorial cerebral herniation and brainstem compression. Studies of patients with severe postoperative hyponatremic encephalopathy have indicated a high incidence of hypoxia, and one fourth of these patients manifested hypercapnic respiratory failure, the expected result of brainstem compression, but three fourths had pulmonary edema as the apparent cause of the hypoxia.[356] Studies of acute hyponatremia after endurance races have similarly shown hypoxia and pulmonary edema in association with brain edema.[149,155] These results therefore suggest the possibility that hypoxia from noncardiogenic pulmonary edema may represent an early sign of developing cerebral edema even before the swelling progresses to the point of brainstem compression and tentorial herniation. Some clinical studies have also suggested that menstruating women[351] and young children[357] may be particularly susceptible to the development of neurologic morbidity and mortality during hyponatremia, especially in the acute postoperative setting.[347] However, other studies failed to corroborate these findings.[358,359] Consequently, the true clinical incidence as well as the underlying mechanisms responsible for these catastrophic cases remains to be determined.

Once the brain has volume-regulated via solute losses, thereby reducing brain edema, neurologic symptoms are not as prominent and may even be virtually absent. This accounts for the fairly common finding of relatively asymptomatic patients despite severe levels of hyponatremia.[17,345] Despite this powerful adaptation process, chronic hyponatremia is frequently associated with neurologic symptomatology, albeit milder and more subtle in nature. A recent report found a high incidence of symptoms in 223 patients

with chronic hyponatremia as a result of thiazide administration: 49% had malaise or lethargy, 47% had dizzy spells, 35% had vomiting, 17% had confusion/obtundation, 17% experienced falls, 6% had headaches, and 0.9% had seizures.[360] Although dizziness can potentially be attributed to a diuretic-induced hypovolemia, symptoms such as confusion, obtundation, and seizures are more consistent with hyponatremic symptomatology. Because thiazide-induced hyponatremia can be readily corrected by stopping the thiazide and/or administering sodium, this represents an ideal situation in which to assess improvement in hyponatremia symptomatology with normalization of the serum [Na^+]; in this study, all of these symptoms improved with correction of the hyponatremia. This is one of the best examples demonstrating reversal of the symptoms associated with chronic hyponatremia by correction of the hyponatremia, because most of the patients in this study did not have underlying comorbidities that might complicate interpretation of their symptoms, as is often the case in patients with SIADH.

Even in patients adjudged to be "asymptomatic" by virtue of a normal neurologic exam, accumulating evidence suggests that there may be previously unrecognized adverse effects as a result of chronic hyponatremia. In one study, 16 patients with hyponatremia secondary to SIADH in the range of 124 to 130 mEq per L demonstrated a significant gait instability that normalized after correction of the hyponatremia to normal ranges.[361] The functional significance of the gait instability was illustrated in a study of 122 patients with a variety of levels of hyponatremia, all judged to be "asymptomatic" at the time of their visit to an emergency department (ED). These patients were compared with 244 age-, sex-, and disease-matched controls also presenting to the same ED during the same time period. Researchers found that 21% of the hyponatremic patients presented to the ED because of a recent fall, compared to only 5% of the controls; this difference was highly significant and remained so after multivariable adjustment.[361] Consequently, this study clearly documented an increased incidence of falls in so-called "asymptomatic" hyponatremic patients.

The clinical significance of the gait instability and fall data were further evaluated in a study that compared 553 patients with fractures to an equal number of age- and sex-matched controls. Hyponatremia was found in 13% of the patients presenting with fractures compared to only 4% of the controls.[362] Similar findings have been reported in a 364 elderly patients with large-bone fractures in New York,[363] and in 1,408 female patients with early chronic renal failure in Ireland.[364] More recently published studies have shown that hyponatremia is associated with increased bone loss in experimental animals and a significant increased odds ratio for osteoporosis of the femoral neck (OR, 2.87; $P < .003$) in humans over the age of 50 in the NHANES III database.[365] Thus, the major clinical significance of chronic hyponatremia may lie in the increased morbidity and mortality associated with falls and fractures in the elderly population.

THERAPY OF HYPOOSMOLAR DISORDERS

Correction of hyponatremia is associated with markedly improved neurologic outcomes in patients with severely symptomatic hyponatremia. In a retrospective review of patients who presented with severe neurologic symptoms and serum [Na^+] less than 125 mEq per L, prompt therapy with isotonic or hypertonic saline resulted in a correction in the range of 20 mEq per L over several days and neurologic recovery in almost all cases. In contrast, in patients who were treated with fluid restriction alone, there was very little correction over the study period (less than 5 mEq per L over 72 hours), and the neurologic outcomes were much worse, with most of these patients either dying or entering a persistently vegetative state.[366] Consequently, based on this and many similar retrospective analyses, prompt therapy to rapidly increase the serum [Na^+] represents the standard of care for treatment of patients presenting with severe life-threatening manifestations of hyponatremia.

As discussed previously, chronic hyponatremia is much less symptomatic as a result of the process of brain volume regulation. Because of this adaptation process, chronic hyponatremia is arguably a condition that clinicians feel they may not need to be as concerned about, which has been reinforced by the common usage of the descriptor asymptomatic hyponatremia for many such patients. However, as discussed previously, it is clear that many such patients very often do have neurologic symptoms, even if milder and more subtle in nature, including headaches, nausea, mood disturbances, depression, difficulty concentrating, slowed reaction times, unstable gait, increased falls, confusion, and disorientation.[361] Consequently, all patients with hyponatremia who manifest any neurologic symptoms that could possibly be related to the hyponatremia should be considered as potential candidates for treatment of their hyponatremia, regardless of the chronicity of the hyponatremia or the level of serum [Na^+].

Initial Evaluation

An approach to the initial evaluation and therapy of patients presenting with hyponatremia is summarized in Figure 70.10. The importance of appropriate initial evaluation and diagnosis cannot be overemphasized, as multiple studies have documented a high frequency of diagnosis- and treatment-related errors in the management of hyponatremic hospitalized patients.[367,368] Once true hypoosmolality is verified, the ECF volume status of the patient should be assessed by careful clinical examination. If fluid retention is present, the treatment of the underlying disease should take precedence over correction of plasma osmolality. Often this involves treatment with diuretics, which should simultaneously improve plasma tonicity by virtue of stimulating excretion of hypotonic urine. If hypovolemia is present, the patient must be considered to have depletion-induced hypoosmolality, in which case volume repletion with isotonic

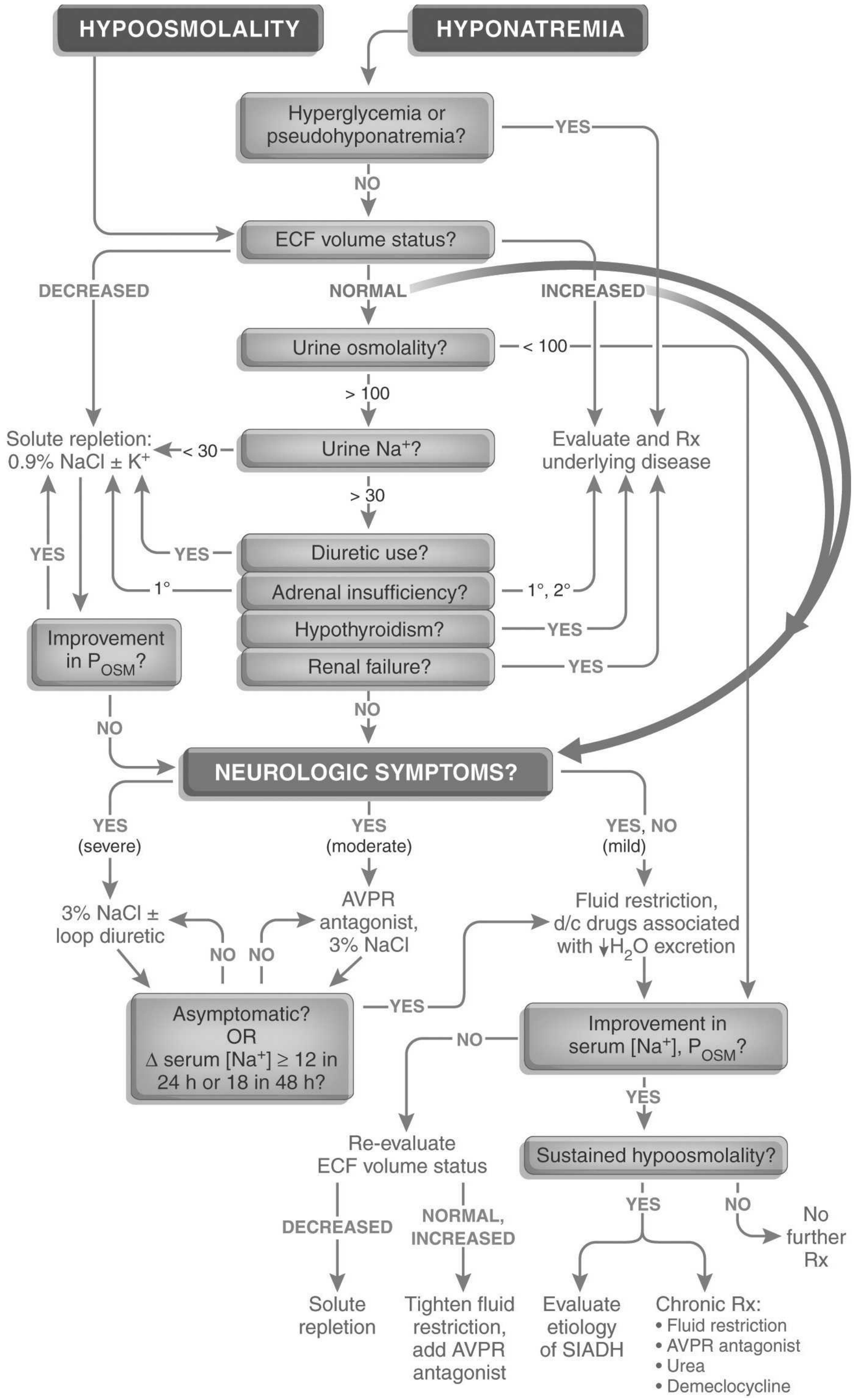

FIGURE 70.10 Schematic summary of the evaluation and therapy of hypoosmolar patients. The *red arrow* in the center emphasizes that the presence of central nervous system dysfunction due to hyponatremia should always be assessed immediately, so that appropriate therapy can be started as soon as possible in symptomatic patients while the outlined diagnostic evaluation is proceeding. (From Verbalis JG. Hyponatremia and hypo-osmolar disorders. In: Greenberg A, Cheung AK, Coffman TM, Falk RJ, Jennette JC, eds. *Primer on Kidney Diseases*. Philadelphia: Saunders Elsevier; 2009: 52–59, with permission.)

saline (0.9% NaCl) at a rate appropriate for the estimated fluid deficit should be initiated (see Chapter 66). If diuretic use is known or suspected, the isotonic saline should be supplemented with potassium (30–40 mEq per L) even if serum [K^+] is not low, because of the propensity of such patients to develop total body potassium depletion. Most often, the hypoosmolar patient is clinically euvolemic, in which case the evaluation should then proceed to the measurement of urine osmolality and urine [Na^+]. Several situations will dictate reconsideration of solute depletion as a potential diagnosis, even in a patient without clinically apparent hypovolemia. These include: (1) a urine [Na^+] less than 30 mEq per L,[89] (2) a history of recent diuretic use, and (3) any suggestion of primary adrenal insufficiency. Whenever a possibility of depletion-induced, rather than dilution-induced, hypoosmolality exists, it is most appropriate to treat the patient initially with isotonic saline, regardless of whether clinical signs of hypovolemia are present or not. An improvement in, and eventual correction of, the hyponatremia verifies solute and volume depletion. On the other hand, if the patient has SIADH rather than solute depletion, no significant harm will be done by administration of a limited volume (e.g., 1–2 L) of isotonic saline, because patients with SIADH simply excrete excess infused or ingested NaCl without significantly changing their plasma osmolality.[1] However, in the absence of an initial positive response, continued infusion of isotonic saline should be avoided because over longer periods of time sufficient free water can be retained to further lower the serum [Na^+].[369]

The approach to patients with euvolemic hypoosmolality will vary according to the clinical situation (see Fig. 70.10). A patient who meets all the essential criteria for SIADH but has a low urine osmolality should be observed on a trial of modest fluid restriction. If the hypoosmolality is attributable to transient SIADH or severe polydipsia, the urine will remain dilute and the plasma osmolality will be fully corrected as free water is excreted. If, however, the patient has the reset osmostat form of the disorder, then the urine will become concentrated at some point before the plasma osmolality and serum [Na^+] return to normal ranges. If either primary or secondary adrenal insufficiency is suspected, glucocorticoid replacement should be initiated immediately after the completion of a rapid ACTH stimulation test.[370,371] A prompt water diuresis after initiation of glucocorticoid treatment strongly supports a diagnosis of glucocorticoid deficiency.[372] However, absence of a quick response does not necessarily negate this diagnosis because several days of glucocorticoid replacement are sometimes required for normalization of plasma osmolality.[90] If hypothyroidism is suspected, thyroid function tests should be conducted including a plasma TSH level; usually replacement therapy is withheld pending these results unless the patient is obviously myxedematous. If renal failure is present in a patient with hypoosmolality, a more extensive evaluation of renal function will be necessary before deciding what course of treatment is most appropriate.

Currently Available Therapies for Treatment of Hyponatremia

Conventional management strategies for hyponatremia range from saline infusion and fluid restriction to pharmacologic measures to adjust fluid balance. Consideration of treatment options should always include an evaluation of the benefits as well as the potential toxicities of any therapy, and must be individualized for each patient.[373] It should always be remembered that sometimes simply stopping treatment with an agent that is associated with hyponatremia is sufficient to reverse a low serum [Na^+] (see Fig. 70.10).

Isotonic Saline

The treatment of choice for depletional hyponatremia (i.e., hypovolemic hyponatremia) is isotonic saline ([Na^+] = 154 mEq per L) to restore ECF volume and ensure adequate organ perfusion. This initial therapy is appropriate for patients who either have clinical signs of hypovolemia, or in whom a urine Na^+ concentration is <30 mEq per L. However, this therapy is ineffective for dilutional hyponatremias such as SIADH,[1] and continued inappropriate administration of isotonic saline to a euvolemic patient may worsen their hyponatremia,[369] and/or cause fluid overload. Although isotonic saline may improve the serum [Na^+] in some patients with hypervolemic hyponatremia, their volume status will generally worsen with this therapy, so isotonic saline should be avoided in such patients unless the hyponatremia is profoundly symptomatic.

Hypertonic Saline

Acute hyponatremia presenting with severe neurologic symptoms is life-threatening, and should be treated promptly with hypertonic solutions, typically 3% NaCl ([Na^+] = 513 mEq per L), as this represents the most reliable method to quickly raise the serum [Na^+]. A continuous infusion of hypertonic NaCl is usually utilized in inpatient settings. Various formulae have been suggested for calculating the initial rate of infusion of hypertonic solutions,[94] but until now there has been no consensus regarding optimal infusion rates of 3% NaCl. One of the simplest methods to estimate an initial 3% NaCl infusion rate utilizes the following relationship[373]:

Patient's weight (kg) × desired correction rate (mEq/L/h) = infusion rate of 3% NaCl (mL/h)

Depending on individual hospital policies, the administration of hypertonic solutions may require special considerations (e.g., placement in the ICU, sign-off by a consultant, etc.), which each clinician needs to be aware of in order to optimize patient care.

An alternative option for more emergent situations is administration of a 100 mL bolus of 3% NaCl, repeated once if there is no clinical improvement within 30 minutes, which has been recommended by a consensus conference organized to develop guidelines for prevention and treatment of EAH.[329] Injecting this amount of hypertonic saline

intravenously raises the serum [Na^+] by an average of 2 to 4 mEq per L, which is well below the recommended maximal daily rate of change of 10 to 12 mEq per 24 hours or 18 mEq per 48 hours.[374] Because the brain can only accommodate an average increase of approximately 8% in brain volume before herniation occurs, quickly increasing the serum [Na^+] by as little as 2 to 4 mEq per L in acute hyponatremia can effectively reduce brain swelling and intracranial pressure.[375]

Many physicians are hesitant to use hypertonic saline in patients with chronic hyponatremia, because it can cause an overly rapid correction of serum sodium levels that can lead to the osmotic demyelination syndrome (ODS),[19] as discussed in the following section. Nonetheless, this remains the treatment of choice for patients with severe neurologic symptoms, even when the time course of the hyponatremia is nonacute or unknown. The administration of hypertonic saline is generally not recommended for most patients with edema-forming disorders because it acts as a volume expander and may exacerbate volume overload; consequently, as with isotonic NaCl, hypertonic saline should be avoided in such patients unless the hyponatremia is profoundly symptomatic.

Fluid Restriction

For patients with chronic hyponatremia, fluid restriction has been the most popular and most widely accepted treatment. When SIADH is present, fluids should generally be limited to 500 to 1,000 mL per 24 hours. Because fluid restriction increases the serum [Na^+] largely by underreplacing the excretion of fluid by the kidneys, some have advocated an initial restriction to 500 mL less than the 24-hour urine output.[376] When instituting a fluid restriction, it is important for the nursing staff and the patient to understand that this includes all fluids that are consumed, not just water. Generally the water content of ingested food is not included in the restriction because this is balanced by insensible water losses (perspiration, exhaled air, feces, etc.), but caution should be exercised with foods that have high fluid concentrations (such as fruits and soups). Restricting fluid intake can be effective when properly applied and managed in selected patients, but the serum [Na^+] generally increases only slowly (1–2 mEq/L/d) even with severe fluid restriction.[1] In addition, this therapy is often poorly tolerated because of an associated increase in thirst leading to poor compliance with long-term therapy. However, fluid restriction is economically favorable, and some patients do respond well to this option.

Fluid restriction should not be used with hypovolemic patients, and is particularly difficult to maintain in patients with very elevated urine osmolalities secondary to high AVP levels; in general, if the sum of urine Na^+ and K^+ exceeds the serum [Na^+], most patients will not respond to a fluid restriction since an electrolyte-free water clearance will be difficult to achieve.[377,378] In addition, fluid restriction is not practical for some patients, particularly including patients in intensive care settings who often require administration of significant volumes of fluids as part of their therapies.

Demeclocycline

Demeclocycline, a tetracycline antibiotic, inhibits adenylyl cyclase activation after AVP binds to its V_2 receptor in the kidney, and thus targets the underlying pathophysiology of SIADH. This therapy is typically used when patients find severe fluid restriction unacceptable and the underlying disorder cannot be corrected. However, demeclocycline is not approved by the U.S. Food and Drug Administration (FDA) to treat hyponatremia, and can cause nephrotoxicity in patients with heart failure and cirrhosis, although this is usually reversible if caught quickly.[379]

Mineralocorticoids

Administration of mineralocorticoids, such as fludrocortisone, has been shown to be useful in a small number of elderly patients.[227] However, the initial studies of SIADH did not show fludrocortisone to be of benefit in these patients, and it carries the risk of fluid overload and hypertension. Consequently, it is rarely used to treat hyponatremia in the United States.

Urea

Administration of urea has been successfully used to treat hyponatremia because it induces osmotic diuresis and augments free water excretion. Effective doses of urea for treatment of hyponatremia are 30 to 90 g daily, usually given in divided doses.[380] Unfortunately, its use is limited because there is no United States Pharmacopeia (USP) formulation for urea, and it is not approved by the FDA for treatment of hyponatremia. As such, urea has not been used extensively in the United States, and there are limited data to support its long-term use. In addition, urea is associated with poor palatability leading to poor patient compliance. However, patients with feeding tubes may be good candidates for urea therapy since palatability is not a concern, and the use of fluid restriction may be difficult in some patients with high obligate intake of fluids as part of their nutritional or medication therapy. Although mild azotemia can be seen with urea therapy, this rarely reaches clinically significant levels.

Furosemide and NaCl

The use of furosemide (20 to 40 mg per day) coupled with a high salt intake (200 mEq per day), which represents an extension of the treatment of acute symptomatic hyponatremia[381] to the chronic management of euvolemic hyponatremia, has also been reported to be successful in selected cases.[382] However, the long-term efficacy and safety of this approach is unknown.

Arginine Vasopressin Receptor Antagonists

Clinicians have used all of the above conventional therapies for hyponatremia over the past decades. However, conventional therapies for hyponatremia, although effective in specific circumstances, are suboptimal for many different

reasons, including variable efficacy, slow responses, intolerable side effects, and serious toxicities. But perhaps the most prominent deficiency of most conventional therapies is that, with the exception of demeclocycline, these therapies do not directly target the underlying cause of almost all dilutional hyponatremias, namely inappropriately elevated plasma AVP levels. A new class of pharmacologic agents, arginine vasopressin receptor (AVPR) antagonists, that directly block AVP-mediated receptor activation have recently been approved by the FDA for treatment of euvolemic and hypervolemic hyponatremia.[383]

Conivaptan and tolvaptan are competitive receptor antagonists of the AVP V_2 (antidiuretic) receptor and have been approved by the FDA for the treatment of euvolemic and hypervolemic hyponatremia. These agents, also known as "vaptans," compete with AVP for binding at its site of action in the kidney, thereby blocking the antidiuresis caused by elevated AVP levels and directly attacking the underlying pathophysiology of dilutional hyponatremia. AVPR antagonists produce electrolyte free water excretion (called aquaresis) without significantly affecting renal sodium and potassium excretion.[384] The overall result is a reduction in body water without natriuresis, which leads to an increase in the serum [Na^+]. One of the major benefits of this class of drugs is that serum [Na^+] is significantly increased by an average of 4 to 8 mEq per L within 24 to 48 hours,[385,386] which is considerably faster than the effects of fluid restriction that can take many days. Also, compliance has not been shown to be a problem for vaptans, whereas this is a major problem with attempted long-term use of fluid restriction.

Conivaptan is FDA-approved for euvolemic and hypervolemic hyponatremia in hospitalized patients. It is available only as an intravenous preparation, and is given as a 20 mg loading dose over 30 minutes, followed by a continuous infusion of 20 or 40 mg per day.[387]Generally, the 20 mg continuous infusion is used for the first 24 hours to gauge the initial response. If the correction of serum [Na^+] is felt to be inadequate (e.g., less than 5 mEq per L), then the infusion rate can be increased to 40 mg per day. Therapy is limited to a maximum duration of 4 days because of drug-interaction effects with other agents metabolized by the CYP3A4 hepatic isoenzyme. Importantly, for conivaptan and all other vaptans, it is critical that the serum [Na^+] concentration is measured frequently during the active phase of correction of the hyponatremia (a minimum of every 6–8 hours for conivaptan, but more frequently in patients with risk factors for development of osmotic demyelination, such as severely low serum [Na^+], malnutrition, alcoholism, liver disease, and hypokalemia[373]). If the correction approaches 12 mEq per L in the first 24 hours, the infusion should be stopped and the patient monitored closely. If the correction exceeds 12 mEq per L, consideration should be given to administering sufficient water, either orally or as intravenous D_5W, to bring the overall correction below 12 mEq per L. The maximum correction limit should be reduced to 8 mEq per L over the first 24 hours in patients with risk factors for development of osmotic demyelination mentioned previously. The most common adverse effects include injection-site reactions, which are generally mild and usually do not lead to treatment discontinuation, headache, thirst, and hypokalemia.[385]

Tolvaptan, an oral AVPR antagonist, is FDA-approved for treatment of dilutional hyponatremias. In contrast to conivaptan, oral administration allows it to be used for both short- and long-term treatment of hyponatremia.[386] Similar to conivaptan, tolvaptan treatment must be initiated in the hospital so that the rate of correction can be monitored carefully. Patients with a serum [Na^+] less than 125 mEq per L are eligible for therapy with tolvaptan as primary therapy; if the serum [Na^+] is equal to or greater than 125 mEq per L, tolvaptan therapy is only indicated if the patient has symptoms that could be attributable to the hyponatremia and the patient is resistant to attempts at fluid restriction.[388] The starting dose of tolvaptan is 15 mg on the first day, and the dose can be titrated to 30 mg and 60 mg at 24-hour intervals if the serum [Na^+] remains less than 135 mEq per L or the increase in serum [Na^+] has been less than 5 mEq per L in the previous 24 hours. As with conivaptan, it is essential that the serum [Na^+] concentration is measured frequently during the active phase of correction of the hyponatremia (a minimum of every 6 to 8 hours, but more frequently in patients with risk factors for development of osmotic demyelination). Limits for safe correction of hyponatremia and methods to compensate for overly rapid corrections are the same as described previously for conivaptan. One additional factor that helps to avoid overly rapid correction with tolvaptan is the recommendation that fluid restriction not be used during the active phase of correction, thereby allowing the patient's thirst to compensate for an overly vigorous aquaresis. Common side effects include dry mouth, thirst, increased urinary frequency, dizziness, nausea, and orthostatic hypotension, which were relatively similar between placebo and tolvaptan groups in clinical trials.[386,388]

Because inducing increased renal fluid excretion via either a diuresis or an aquaresis can cause or worsen hypotension in patients with hypovolemic hyponatremia, vaptans are contraindicated in this patient population.[373] However, clinically significant hypotension was not observed in either the conivaptan or tolvaptan clinical trials in euvolemic and hypervolemic hyponatremic patients. Although vaptans are not contraindicated with decreased renal function, these agents generally will not be effective if the serum creatinine is greater than 2.5 mg per dL.

Osmotic Demyelination Syndrome

Before deciding on the therapy for any hyponatremic patient, the possibility of producing harm from correction of the hyponatremia must be carefully considered. Despite the obvious survival advantages afforded by brain volume regulation in response to hyponatremia, every adaptation made by the body in response to a perturbation of homeostasis bears within it the potential to create a new set of problems, and this is true for brain volume regulation as well. Over the last several decades it has become apparent that the demyelinating disease of central pontine myelinolysis (CPM)

occurs with a significantly higher incidence in patients with hyponatremia,[389–391] and in both animal[392–396] and human studies[19,397,398] brain demyelination has clearly been shown to be associated with the correction of existing hyponatremia rather than simply to the presence of severe hyponatremia itself. Because demyelination following correction of hyponatremia has a unique etiology and frequently occurs in other white matter areas of the brain in addition to the pons, the occurrence of demyelination in hyponatremic patients has been named the osmotic demyelination syndrome (ODS).[19] Although the mechanism(s) by which correction of hyponatremia leads to brain demyelination remain under investigation, this pathologic disorder likely is precipitated by the brain dehydration that has been demonstrated to occur following correction of serum [Na^+] toward normal ranges in animal models of chronic hyponatremia. Because the degree of osmotic brain shrinkage is greater in animals that are maintained chronically hyponatremic than in normonatremic animals undergoing similar increases in plasma osmolality,[196,394,399] by analogy the brains of human patients adapted to hyponatremia are likely to be particularly susceptible to dehydration following subsequent increases in osmolality, which in turn can lead to pathologic demyelination in some patients. MRI studies have shown that chronic hypoosmolality predisposes rats to opening of the blood–brain barrier following rapid correction of hyponatremia,[400] and that the disruption of the blood–brain barrier is highly correlated with subsequent demyelination[401]; a potential mechanism by which blood–brain barrier disruption might lead to subsequent myelinolysis is via an influx of complement, which is toxic to the oligodendrocytes that manufacture and maintain myelin sheaths of neurons, into the brain.[402]

Although there has been considerable debate in the literature regarding the parameters of correction of hyponatremia associated with an increased risk of myelinolysis, studies in both patients[403–405] and experimental animals[394–396] support the notion that both the rate of correction of hyponatremia and the total magnitude of the correction over the first few days likely represent significant factors that increase the risk of demyelination. Studies in rats have shown that the initial rate of correction of hyponatremia may not be important for the development of demyelinative lesions as long as the total magnitude of the correction remains less than 20 mEq per L in 24 hours,[406] which supports clinical data indicating that magnitude of correction represents the major risk factor related to subsequent neurologic morbidity and mortality. There is still some disagreement as to the actual magnitude of correction at which patients are at risk for ODS; initial reports implicated increases in serum [Na^+] greater than 25 mEq per L over the first 24 to 48 hours of treatment,[403] whereas later studies have suggested occurrence of ODS with even lesser increases in serum [Na^+] of greater than 12 mEq per L in 24 hours or greater than 18 mEq per L in 48 hours.[374] Although overcorrection of hyponatremia to supranormal levels is also clearly a risk factor for neurologic deterioration, it is important to note that both clinical and experimental studies have found that demyelination occurred following corrections to serum [Na^+] levels still below normal ranges. Regardless of the level of increase in serum [Na^+] at which ODS occurs, the methods used to correct hyponatremia do not appear to have any significant bearing on the production of brain demyelination, since both experimental studies[396] and clinical reports[19,407–409] have demonstrated that demyelination can occur independent of the method used to correct the hyponatremia.

Other factors also can clearly influence the susceptibility to demyelination following correction of hyponatremia. Perhaps most importantly are the severity and the duration of the preexisting hyponatremia. Both of these risk factors likely relate to the degree of brain volume regulation that has occurred prior to the correction: the more severe the hyponatremia and the longer it has been maintained, the greater the degree of solute loss that will have occurred during the process of brain volume regulation. As larger amounts of solute are lost, the ability of the brain to buffer subsequent increases in plasma osmolality is impaired, resulting in greater degrees of brain dehydration as serum [Na^+] is later raised, which in turn can lead to brain demyelination via mechanisms discussed earlier. Clinical implications of this pathophysiologic mechanism are that ODS should not occur in cases of either mild or very acute hyponatremia. Both of these findings have been found to be true. ODS has only rarely been reported in patients with a starting serum [Na^+] greater than 120 mEq per L,[19,374,410] and also does not appear to occur in most patients with psychogenic polydipsia who are well known to develop hyponatremia acutely from episodes of massive water ingestion followed by rapid correction as they diurese the excess fluid.[303] There are also some independent risk factors for the occurrence of CPM, particularly chronic alcoholism and malnutrition, which led to the original description of this disorder in 1959.[411] Although no studies to date have clearly documented interactive effects between these risk factors and ODS, it seems likely that the threshold for increases in serum [Na^+] that increase the risk for ODS will be lower in alcoholic and malnourished patients, and reports of myelinolysis in patients with chronic alcoholism in whom the rate of correction stayed within the recommended guidelines supports this likelihood.[412,413] Interestingly, one factor that appears to protect hyponatremic patients from myelinolysis following rapid correction of hyponatremia is uremia. Although uremic patients on dialysis frequently have large swings of serum [Na^+], only rare cases of osmotically induced demyelination have been reported in this group.[414] A study in rats showed that azotemic rats were able to sustain large increases in serum [Na^+] without brain damage, purportedly because the urea acts as an intracellular osmolyte to stabilize intracellular volume and thereby reduces the degree of brain dehydration produced following rapid correction of hyponatremia.[415]

Several other aspects of this unique disease deserve emphasis. First, apropos the widespread nature of the neuropathologic lesions, a much broader range of neurologic disorders is now being reported in patients following correction

of hyponatremia, including cognitive, behavioral, and neuropsychiatric disorders, presumably as a result of demyelination in subcortical, corpus callosal, and hippocampal white matter,[416,417] and movement disorders, as a result of demyelination in the basal ganglia.[418–420] Second, MRI scans often fail to demonstrate the characteristic demyelinative lesions in many cases because scans are usually negative until sufficient time has passed (generally 3–4 weeks) after the correction of hyponatremia and the onset of neurologic symptoms.[421–423] Consequently, the presence of positive MRI findings strongly (though not unequivocally[424]) supports a diagnosis of ODS, but the absence of radiologic findings can never eliminate the possibility of this disorder. Third, although most cases of ODS have been associated with rapid correction of hyponatremia, the disorder has also been reported with severe hypernatremia in both animal models[425] and patients.[426] This is consistent with the hypothesis that brain dehydration with subsequent disruption of the blood–brain barrier is related to the pathogenesis of the demyelinative process.[401,402] Finally, it is clear that given our present knowledge, we cannot predict with any degree of certainty which patients will develop demyelination regardless of the parameters used to correct hyponatremia. Many patients undergo very rapid and large corrections of their serum [Na^+] without subsequent neurologic complications,[427] as is true of experimental animals as well.[396,406] Consequently, overly rapid correction of hyponatremia should be viewed as a factor that puts patients at risk for ODS, but does not inevitably precipitate this disorder.

Hyponatremia Treatment Guidelines

Based on the previous discussions of hyponatremic encephalopathy and the osmotic demyelination syndrome, it follows that optimal treatment of hyponatremic patients must entail balancing the risks of hyponatremia against the risks of correction for each patient individually. Although individual variability in response is great, and consequently one cannot always accurately predict which patients will develop neurologic complications from either hyponatremia or its correction, consensus guidelines for treating hypoosmolar patients allow a rational approach to minimizing the risks of both these complications. Implicit in these guidelines is the realization that treatment must be individualized and tailored to each patient's clinical presentation: appropriate therapy for one hyponatremic patient may be inappropriate for another despite equivalent degrees of hypoosmolality.[5,428] To accomplish this, three factors should be taken into consideration when making a treatment decision in a hypoosmolar patient: (1) the severity of the hyponatremia, (2) the duration of the hyponatremia, and (3) the patient's neurologic symptomatology. The importance of duration and symptomatology both relate to how well the brain has adapted to the hyponatremia and consequently its degree of risk for subsequent demyelination with rapid correction. However, of these factors, the severity of the hypoosmolality is the single most important consideration. The red arrow in Figure 70.10 emphasizes that hypoosmolar patients should always be evaluated quickly for the presence of neurologic symptoms so that appropriate therapy can be initiated, if indicated, even whereas other results of the diagnostic evaluation are still pending.

Although various authors have published recommendations on the treatment of hyponatremia,[94,348,373,429,430] no standardized treatment algorithms have yet been widely accepted. A synthesis of existing expert recommendations for treatment of hyponatremia is illustrated in Figure 70.11.

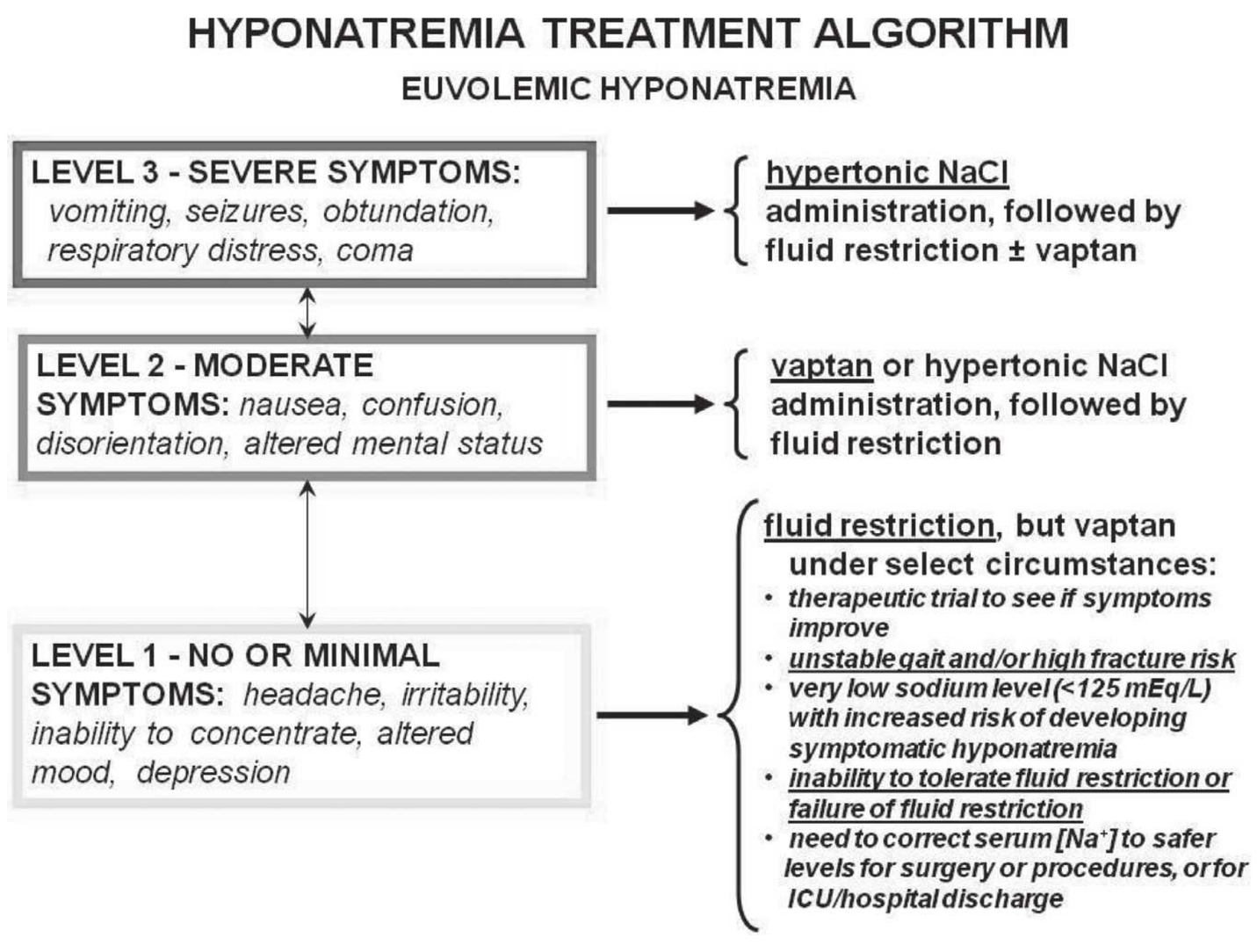

FIGURE 70.11 Algorithm for treatment of patients with euvolemic hyponatremia based on their presenting symptoms. The *arrows* between the symptom boxes indicate movement of patients between different symptom levels. (Modified from Verbalis JG. Managing hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion. *Endocrinol Nutr.* 2010;57 Suppl 2:30–40, with permission.)

This treatment algorithm is based primarily on the symptomatology of hyponatremic patients, rather than the serum [Na^+] or on the chronicity of the hyponatremia, which is often difficult to ascertain. A careful neurologic history and assessment should always be done to identify potential causes for the patient's symptoms other than hyponatremia, although it will not always be possible to exclude an additive contribution from the hyponatremia to an underlying neurologic condition. In this algorithm, patients are divided into three groups based on their presenting symptoms.

Level 1 (Severe) Symptoms

The presence of seizures, coma, respiratory arrest, obtundation, and vomiting usually indicate a more acute onset or worsening of hyponatremia requiring immediate active treatment. Therapies that will quickly raise serum sodium levels are required to reduce cerebral edema and decrease the risk of potentially fatal herniation.

Level 2 (Moderate) Symptoms

Nausea, confusion, disorientation, and altered mental status are more moderate hyponatremic symptoms. These symptoms may be either a manifestation of chronic or acute hyponatremia, but allow time to elaborate a more deliberate approach to treatment.

Level 3 (Mild) Symptoms

This group consists of minimal symptoms such as a headache, irritability, inability to concentrate, altered mood, and depression, to a virtual absence of discernible symptoms, and indicate that the patient may have chronic or slowly evolving hyponatremia. These symptoms necessitate a more cautious and deliberate approach, especially when patients have underlying co-morbidities.

Patients with severe symptoms (level 1) should be treated with hypertonic saline as first-line therapy, followed by fluid restriction with or without AVPR antagonist therapy. Patients with moderate symptoms will benefit from a regimen of vaptan therapy or limited hypertonic saline administration, followed by fluid restriction or long-term vaptan therapy. Although moderate neurologic symptoms can indicate that a patient is in an early stage of acute hyponatremia, they more often indicate a chronically hyponatremic state with sufficient brain volume adaptation to prevent marked symptomatology from cerebral edema. Regardless, close monitoring of these patients in a hospital setting is warranted until the symptoms improve or stabilize. Patients with no or minimal symptoms should be managed initially with fluid restriction, although subsequent treatment with vaptans may be appropriate for a wide range of specific clinical conditions, foremost of which is the failure to improve the serum [Na^+] despite reasonable attempts at fluid restriction (see Fig. 70.11).

A special case is when rapid correction of hyponatremia occurs at an undesirably rapid rate as a result of the onset of a spontaneous aquaresis. This can occur following cessation of desmopressin therapy in a patient who has become hyponatremic, replacement of glucocorticoids in a patient with adrenal insufficiency, replacement of solutes in a patient with diuretic-induced hyponatremia, or spontaneous resolution of transient SIADH. Brain damage from ODS can clearly ensue in this setting if the preceding period of hyponatremia has been of sufficient duration (usually greater than 48 hours) to allow brain volume regulation to occur. If the previously discussed correction parameters have been exceeded and the correction is proceeding more rapidly than planned (usually because of continued excretion of hypotonic urine), the pathologic events leading to demyelination can be reversed by readministration of hypotonic fluids and desmopressin. Efficacy of this approach is suggested both from animal studies[431] as well as reports in humans,[429,432] even when patients are overtly symptomatic.[433]

Although this classification is based on presenting symptoms at the time of initial evaluation, it should be remembered that in some cases patients initially exhibit more moderate symptoms because they are in the early stages of hyponatremia. In addition, some patients with minimal symptoms are prone to develop more symptomatic hyponatremia during periods of increased fluid ingestion. In support of this, approximately 70% of 31 patients presenting to a university hospital with symptomatic hyponatremia and a mean serum [Na^+] of 119 mEq per L had preexisting asymptomatic hyponatremia as their most common risk factor identified.[434] Consequently, therapy of hyponatremia should also be considered to prevent progression from lower to higher levels of symptomatic hyponatremia, particularly in patients with a past history of repeated presentations for symptomatic hyponatremia.

Monitoring the Serum [Na^+] in Hyponatremic Patients

Regardless of the initial rate of correction chosen, acute treatment should be interrupted once any of three endpoints is reached: (1) the patient's symptoms are abolished, (2) a safe serum [Na^+] (generally greater than 120 mEq per L) is achieved, or (3) a total magnitude of correction of 12 mEq per L in 24 h or 18 mEq per L in 48 h is achieved (see Fig. 70.10). Once any of these endpoints is reached, the active correction should be stopped and the patient treated with slower acting therapies, such as oral rehydration or fluid restriction, depending on the etiology of the hypoosmolality. It follows from these recommendations that serum [Na^+] levels must be carefully monitored at frequent intervals during the active phases of treatment to adjust therapy to keep the correction within these maximum limits.

The frequency of serum [Na^+] monitoring is dependent on both the severity of the hyponatremia and the therapy chosen. In all hyponatremic patients neurologic symptomatology should be carefully assessed very early in the diagnostic evaluation to evaluate the symptomatic severity of

the hyponatremia and to determine whether the patient requires more urgent therapy. All patients undergoing active treatment with hypertonic saline for level 1 or level 2 symptomatic hyponatremia should have frequent monitoring of serum [Na^+] and ECF volume status (every 2–4 hours) to ensure that the serum [Na^+] does not exceeded the recommended levels during the active phase of correction,[373] since overly rapid correction of serum sodium can cause ODS.[19] Patients treated with vaptans for level 2 or level 3 symptoms should have serum [Na^+] monitored every 6 to 8 hours during the active phase of correction, which will generally be the first 24 to 48 hours of therapy. Importantly, ODS has not yet been reported either in clinical trials or with therapeutic use of any vaptan to date. In patients with a stable level of serum [Na^+] treated with fluid restriction or therapies other than hypertonic saline, measurement of serum [Na^+] daily is generally sufficient, because levels will not change that quickly in the absence of active therapy or large changes in fluid intake or administration.

Management of Overly Rapid Correction of Hyponatremia

Despite the best attempts at treating hyponatremia, occasional patients will exceed the recommended maximal limits of correction of 12 mEq per L in 24 hours or 18 mEq per L in 48 hours. As discussed previously, this is common with rapid corrections as a result of spontaneous aquaresis. However, overly rapid correction also has been found to accompany corrections of thiazide-induced hyponatremia and use of hypertonic saline.[435] Regardless of how it occurs, the occurrence of an overly rapid correction requires active intervention to decrease the risk of ODS.[436]The only exceptions to this are cases in which the hyponatremia is known to be acute (i.e., less than 48 hours duration), in which case complete brain volume regulation has not occurred and patients do not appear to be at risk of ODS with rapid correction of their serum [Na^+] to normal levels.[303] For any patient with chronic hyponatremia who is found to be correcting overly rapidly, attempts should be made to prevent further correction and to bring the correction back to safe limits for that patient. In most patients this will be the recommended maximal limits of correction of 12 mEq per L in 24 hours or 18 mEq per L in 48 hours,[374] but in patients at high risk of ODS (severely low serum [Na^+] less than 105 mEq per L, malnutrition, alcoholism, liver disease, or hypokalemia), the maximal correction should not exceed 8 mEq per L in 24 hours.[373]

In order to prevent further correction, all active therapies should be stopped, including saline infusions and pharmacologic therapies such as vaptans. However this will not be sufficient if the patient is undergoing a spontaneous aquaresis because the ongoing water excretion will cause continued increases in the serum [Na^+]. One option in such cases is to give water, orally or intravenously as 5% dextrose solution, at a volume that equals the hourly urine output. However, this can be difficult to do, since urine output can reach 800 to 1,000 mL per hour in the setting of suppressed AVP levels. An alternative is to give dDAVP (1 to 2 μg subcutaneously) in order to stop the aquaresis, an approach that has been successfully employed.[437] As each dose of dDAVP wears off (generally in 6–12 hours) and urine output increases, a decision will need to be made regarding re-dosing based on the desired further correction of the serum [Na^+]. With the combined use of dDAVP and water administration, it is possible to control corrections of hyponatremia to within acceptable limits in virtually all patients.

In cases in which an overcorrection has already occurred, consideration should be given to lowering the serum [Na^+] back to the maximally desired correction in that patient, again using water administration and/or dDAVP. Animal models have suggested that lowering the serum [Na^+] after overcorrection can prevent subsequent brain damage from occurring,[431,438] and this would be consistent with the occurrence of a delayed immunologic demyelination as a result of complement influx into the brain following a sustained blood–brain barrier disruption.[402] A case report in which delayed lowering of serum [Na^+] was associated with a reversal of symptoms suggestive of early myelinolysis also supports this as a potential therapy in similar cases.[439] Experimental studies in animals have shown that administration of high-dose glucocorticoids can prevent the development of osmotic demyelination after rapid correction of hyponatremia in rats,[440] again likely via stabilization of the blood–brain barrier to prevent or minimize disruption. Although controlled clinical studies with glucocorticoids have not yet been done in humans, it would seem prudent to employ this relatively benign intervention in cases where a correction of hyponatremia in excess of current guidelines has already occurred, or prior to correction in cases at high risk for development of ODS. More recent promising experimental studies suggest that the drug minocycline may be able to prevent or reduce demyelination following rapid correction of hyponatremia by inhibiting brain microglial activation[441,442]; controlled clinical studies will be necessary to determine the dosing, efficacy, and safety of this drug in humans.

Long-term Treatment of Chronic Hyponatremia

Some patients will benefit from continued treatment of hyponatremia following discharge from the hospital. In many cases, this will consist of a continued fluid restriction. However, as discussed previously, long-term compliance with this therapy is poor due to the increased thirst that occurs with more severe degrees of fluid restriction. For selected patients who have responded to tolvaptan in the hospital, consideration should be given to continuing the treatment as an outpatient after discharge. In patients with established chronic hyponatremia, tolvaptan has been shown to be effective at maintaining a normal [Na^+] for as long as 4 years of continued daily therapy.[443] However, many patients with inpatient hyponatremia will have a

transient form of SIADH without any need for long-term therapy. In the conivaptan open-label study, approximately 70% of patients treated as an inpatient for 4 days had normal serum [Na^+] concentrations 7 and 30 days after cessation of the vaptan therapy in the absence of chronic therapy for hyponatremia. Selection of which patients with inpatient hyponatremia are candidates for long-term therapy should be based on the etiology of the SIADH. Figure 70.12 shows estimates of the relative probability that patients with different causes of SIADH will have persistent hyponatremia that may benefit from long-term treatment with tolvaptan following discharge from the hospital. Nonetheless, for any individual patient this simply represents an estimate of the likelihood of requiring long-term therapy. In all cases, consideration should be given to a trial of stopping the drug at 2 to 4 weeks following discharge to determine if hyponatremia is still present.

A reasonable period of tolvaptan cessation to evaluate the presence of continued SIADH is 7 days, since this period was sufficient for demonstration of a recurrence of hyponatremia in the tolvaptan clinical trials.[386,443] Serum [Na^+] should be monitored every 2 to 3 days following cessation of tolvaptan so that the drug can be resumed as quickly as possible in those patients with recurrent hyponatremia because the longer the patient is hyponatremic the greater the risk of subsequent osmotic demyelination with overly rapid correction of the low serum [Na^+].

Future of Hyponatremia Treatment

Guidelines for the appropriate treatment of hyponatremia, and particularly the role of vaptans, are still evolving, and will undoubtedly change substantially over the next several years. Of special interest will be studies to assess whether more effective treatment of hyponatremia can reduce the incidence of falls and fractures in elderly patients, whether more effective treatment of hyponatremia can reduce utilization of healthcare resources for both inpatients and outpatients with hyponatremia, and whether more effective treatment of hyponatremia can reduce the markedly increased morbidity and mortality of patients with hyponatremia across multiple disease states. A potential role for vaptans in the treatment of heart failure has already been studied. A large trial in patients with heart failure (EVEREST) demonstrated short-term improvement in dyspnea, but no long-term survival benefit.[444] However, this trial was not powered to evaluate the outcomes of hyponatremic patients with heart failure. Consequently, the potential therapeutic role of AVPR antagonists in the treatment of water-retaining disorders must await further studies specifically designed to assess specific clinical outcomes of hyponatremic patients treated with vaptans,

Etiology of SIADH	Likely duration of SIADH*	Relative risk of chronic SIADH
Tumors producing vasopressin ectopically (small-cell lung carcinoma, head and neck carcinoma)	Indefinite	High
Drug-induced, with continuation of offending agent (carbamazepine, SSRI)	Duration of drug therapy	
Brain tumors	Indefinite	
Idiopathic (senile)	Indefinite	
Subarachnoid hemorrhage	1–4 weeks	
Stroke	1–2 weeks	
Inflammatory brain lesions	Dependent on response to therapy	Medium
Respiratory failure (chronic obstructive lung disease)	Dependent on response to therapy	
HIV infection	Dependent on response to therapy	
Traumatic brain injury	2–7 days to indefinite	
Drug-induced, with cessation of offending agent	Duration of drug therapy	
Pneumonia	2–5 days	
Nausea, pain, prolonged exercise	Variable depending on cause	
Postoperative hyponatremia	2–3 days postoperatively	Low

*Time frames are based on clinical experience.

FIGURE 70.12 Estimated probability of the need for long-term treatment of SIADH depending on the underlying etiology of hyponatremia. The time frames of likely duration of SIADH are estimates based on clinical experience with these etiologies. (Modified from Verbalis JG. Managing hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion. *Endocrinol Nutr.* 2010;57 Suppl 2:30–40, with permission.)

as well as increased clinical experience to better delineate efficacies as well as potential toxicities of all treatments for hyponatremia. Nonetheless, it is abundantly clear that the vaptans clearly have ushered in a new era in the evaluation and treatment of hyponatremic disorders.

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