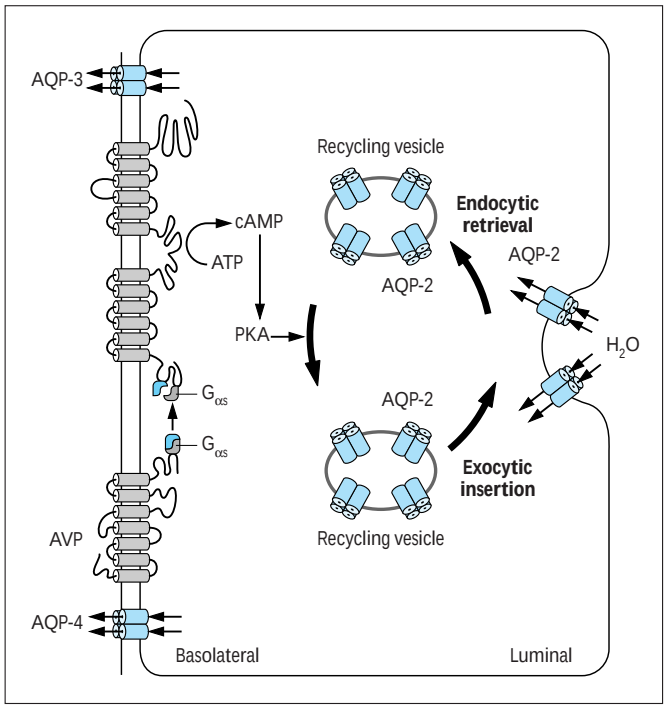

FIGURE 1-9

Intracellular action of antidiuretic hormone. The multiple actions of vasopressin can be accounted for by its interaction with the V2 receptor found in the kidney. After stimulation, vasopressin binds to the V2 receptor on the basolateral membrane of the collecting duct cell. This interaction of vasopressin with the V2 receptor leads to increased adenylate cyclase activity via the stimulatory G protein (Gs), which catalyzes the formation of cyclic adenosine 3', 5'-monophosphate (cAMP) from adenosine triphosphate (ATP). In turn, cAMP activates a serine threonine kinase, protein kinase A (PKA). Cytoplasmic vesicles carrying the water channel proteins migrate through the cell in response to this phosphorylation process and fuse with the apical membrane in response to increasing vasopressin binding, thus increasing water permeability of the collecting duct cells. These water channels are recyled by endocytosis once the vasopressin is removed. The water channel responsible for the high water permeability of the luminal membrane in response to vasopressin has recently been cloned and designated as aquaporin-2 (AQP-2) [8]. The other members of the aquaporin family, AQP-3 and AQP-4 are located on the basolateral membranes and are probably involved in water exit from the cell. The molecular biology of these channels and of receptors responsible for vasopressin action have contributed to the understanding of the syndromes of genetically transmitted and acquired forms of vasopressin resistance. AVP—arginine vasopressin.

AQUAPORINS AND THEIR CHARACTERISTICS

	AQP-1	AQP-2	AQP-3	AQP-4
Size (amino acids)	269	271	285	301
Permeability to small solutes	No	No	Urea glycerol	No
Regulation by antidiurectic hormone	No	Yes	No	No
Site	Proximal tubules; descending thin limb	Collecting duct; principal cells	Medullary collecting duct; colon	Hypothalamic—supraoptic, paraventricular nuclei; ependymal, granular, and Purkinje cells
Cellular localization	Apical and basolateral membrane	Apical membrane and intracellular vesicles	Basolateral membrane	Basolateral membrane of the prinicpal cells
Mutant phenotype	Normal	Nephrogenic diabetes insipidus	Unknown	Unknown

FIGURE 1-10

Aquaporins and their characteristics. An ever growing family of aquaporin (AQP) channels are being described. So far, about seven different channels have been cloned and characterized; however, only four have been found to have any definite physiologic role.

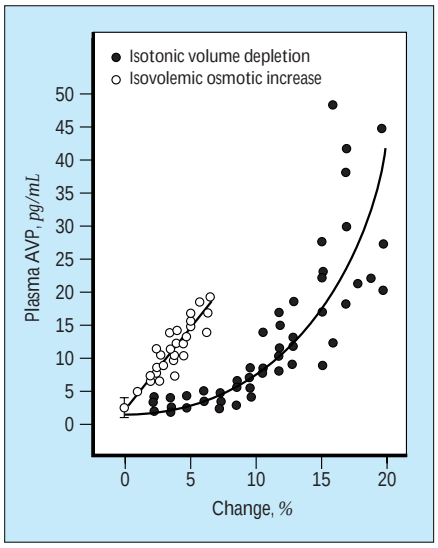

FIGURE 1-11

Osmotic and nonosmotic regulation of antidiuretic hormone (ADH) secretion. ADH is secreted in response to changes in osmolality and in circulating arterial volume. The "osmoreceptor" cells are located in the anterior hypothalamus close to the supraoptic nuclei. Aquaporin-4 (AQP-4), a candidate osmoreceptor, is a member of the water channel family that was recently cloned and characterized and is found in abundance in these neurons. The osmoreceptors are sensitive to changes in plasma osmolality of as little as 1%. In humans, the osmotic threshold for ADH release is 280 to 290 mOsm/kg. This system is so efficient that the plasma osmolality usually does not vary by more than 1% to 2% despite wide fluctuations in water intake [9]. There are several other nonosmotic stimuli for ADH secretion. In conditions of decreased arterial circulating volume (*eg*, heart failure, cirrhosis, vomiting), decrease in inhibitory parasympathetic afferents in the carotid sinus baroreceptors affects ADH secretion. Other nonosmotic stimuli include nausea, which can lead to a 500-fold rise in circulating ADH levels, postoperative pain, and pregnancy. Much higher ADH levels can be achieved with hypovolemia than with hyperosmolarity, although a large fall in blood volume is required before this response is initiated. In the maintenance of tonicity the interplay of these homeostatic mechanisms also involves the thirst mechanism, that under normal conditions, causes either intake or exclusion of water in an effort to restore serum osmolality to normal.

Control of Water Balance and Serum Sodium Concentration

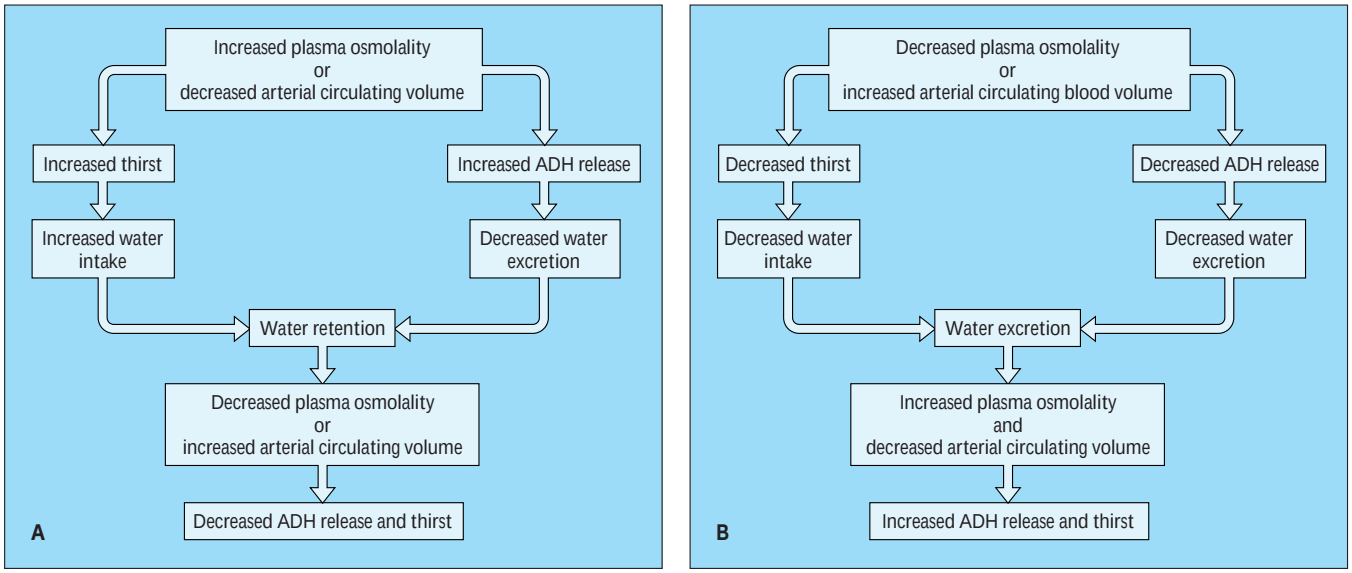

FIGURE 1-12

Pathways of water balance (conservation, **A**, and excretion, **B**). In humans and other terrestrial animals, the thirst mechanism plays an important role in water (H_2O) balance. Hypertonicity is the most potent stimulus for thirst: only 2% to 3 % changes in plasma osmolality produce a strong desire to drink water. This absolute level of osmolality at which the sensation of thirst arises in healthy persons, called the *osmotic threshold for thirst*, usually averages about 290 to 295 mOsm/kg H_2O (approximately 10 mOsm/kg H_2O above that of antidiuretic hormone [ADH] release). The so-called thirst center is located close to the osmoreceptors but is anatomically distinct. Between the limits imposed by the osmotic thresholds for thirst and ADH release, plasma osmolality may be regulated still more precisely by small osmoregulated adjustments in urine flow and water intake. The exact level at which balance occurs depends on various factors such as insensible losses through skin and lungs, and the gains incurred from eating, normal drinking, and fat metabolism. In general, overall intake and output come into balance at a plasma osmolality of 288 mOsm/kg, roughly halfway between the thresholds for ADH release and thirst [10].

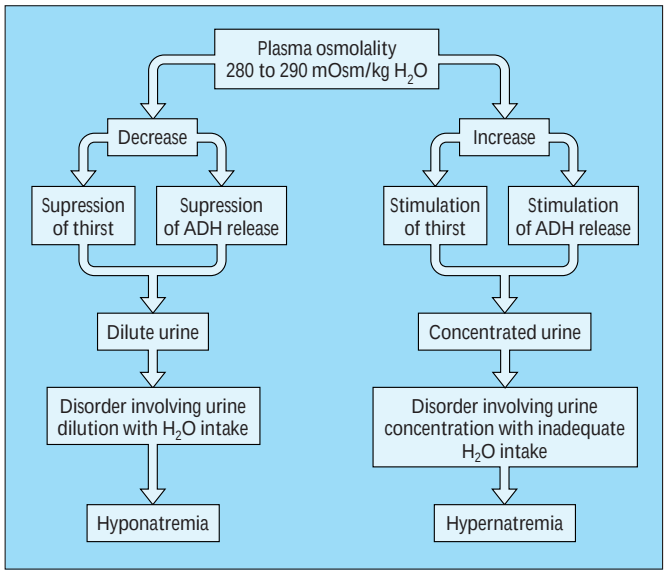

FIGURE 1-13

Pathogenesis of dysnatremias. The countercurrent mechanism of the kidneys in concert with the hypothalamic osmoreceptors via antidiuretic hormone (ADH) secretion maintain a very finely tuned balance of water (H_2O). A defect in the urine-diluting capacity with continued H_2O intake results in hyponatremia. Conversely, a defect in urine concentration with inadequate H_2O intake culminates in hypernatremia. Hyponatremia reflects a disturbance in homeostatic mechanisms characterized by excess total body H_2O relative to total body sodium, and hypernatremia reflects a deficiency of total body H_2O relative to total body sodium [11]. (*From* Halterman and Berl [12]; with permission.)

Approach to the Hyponatremic Patient

EFFECTS OF OSMOTICALLY ACTIVE SUBSTANCES ON SERUM SODIUM

Substances the increase osmolality without changing serum sodium	Substances that increase osmolality and decrease serum sodium (translocational hyponatremia)
Urea	Glucose
Ethanol	Mannitol
Ethylene glycol	Glycine
Isopropyl alcohol	Maltose
Methanol	

FIGURE 1-14

Evaluation of a hyponatremic patient: effects of osmotically active substances on serum sodium. In the evaluation of a hyponatremic patient, a determination should be made about whether hyponatremia is truly hypo-osmotic and not a consequence of *translocational* or *pseudohyponatremia*, since, in most but not all situations, hyponatremia reflects hypo-osmolality.

The nature of the solute plays an important role in determining whether or not there is an increase in measured osmolality or an actual increase in effective osmolality. Solutes that are permeable across cell membranes (*eg*, urea, methanol, ethanol, and ethylene glycol) do not cause water movement and cause hypertonicity without causing cell dehydration. Typical examples are an uremic patient with a high blood urea nitrogen value and an ethanol-intoxicated person. On the other hand, in a patient with diabetic ketoacidosis who is insulinopenic the glucose is not permeant across cell membranes and, by its presence in the extracellular fluid, causes water to move from the cells to extracellular space, thus leading to cell dehydration and lowering serum sodium. This can be viewed as translocational at the cellular level, as the serum sodium level does not reflect changes in total body water but rather movement of water from intracellular to extracellular space. Glycine is used as an irrigant solution during transurethral resection of the prostate and in endometrial surgery. Pseudohyponatremia occurs when the solid phase of plasma (usually 6% to 8%) is much increased by large increments of either lipids or proteins (*eg*, in hypertriglyceridemia or paraproteinemias).