At a 10% loss of body fluid, the patient will show signs of confusion, distress, and hallucinations and at 20%, death will occur.

—Poul Astrup, in Salt and Water in Culture and Medicine, 1993

Background Basics

Body fluid compartments
Protein structure
pH and buffers
Membrane transport
Membrane recycling
Polarized epithelial cells
Second messenger systems
Peptide hormones
Posterior pituitary hormones
Steroid hormones
Control of blood pressure
CO2 excretion by lungs
Carbonic anhydrase
Osmolarity and tonicity
Glomerular filtration rate

Fluid and Electrolyte Homeostasis

ECF Osmolarity Affects Cell Volume
Multiple Systems Integrate Fluid and Electrolyte Balance

Water Balance

Daily Water Intake and Excretion Are Balanced
The Kidneys Conserve Water
The Renal Medulla Creates Concentrated Urine
Vasopressin Controls Water Reabsorption
Blood Volume and Osmolarity Activate Osmoreceptors
The Loop of Henle Is a Countercurrent Multiplier

Sodium Balance and ECF Volume

Aldosterone Controls Sodium Balance
Low Blood Pressure Stimulates Aldosterone Secretion
ANG II Has Many Effects
ANP Promotes Na+ and Water Excretion

Potassium Balance

Behavioral Mechanisms in Salt and Water Balance

Drinking Replaces Fluid Loss
Low Na+ Stimulates Salt Appetite
Avoidance Behaviors Help Prevent Dehydration

Integrated Control of Volume and Osmolarity

Osmolarity and Volume Can Change Independently
Dehydration Triggers Homeostatic Responses

Acid-Base Balance

pH Changes Can Denature Proteins
Acids and Bases in the Body Come from Many Sources
pH Homeostasis Depends on Buffers, Lungs, and Kidneys
Buffer Systems Include Proteins, Phosphate Ions, and HCO3-
Ventilation Can Compensate for pH Disturbances
Kidneys Use Ammonia and Phosphate Buffers
The Proximal Tubule Excretes H+ and Reabsorbs HCO3-
The Distal Nephron Controls Acid Excretion
Acid-Base Disturbances May Be Respiratory or Metabolic

From Chapter 20 of Human Physiology: An Integrated Approach, Sixth Edition. Dee Unglaub Silverthorn. Copyright © 2013 by Pearson Education, Inc. All rights reserved.
The American businesswoman in Tokyo finished her workout and stopped at the snack bar of the fitness club to ask for a sports drink. The attendant handed her a bottle labeled “Pocari Sweat®.” Although the thought of drinking sweat is not very appealing, the physiological basis for the name is sound.

During exercise, the body secretes sweat, a dilute solution of water and ions, particularly Na⁺, K⁺, and Cl⁻. To maintain homeostasis, the body must replace any substances it has lost to the external environment. For this reason, the replacement fluid a person consumes after exercise should resemble sweat.

In this chapter, we explore how humans maintain salt and water balance, also known as fluid and electrolyte balance. The homeostatic control mechanisms for fluid and electrolyte balance in the body are aimed at maintaining four parameters: fluid volume, osmolarity, the concentrations of individual ions, and pH.

**Fluid and Electrolyte Homeostasis**

The human body is in a state of constant flux. Over the course of a day we ingest about 2 liters of fluid that contains 6–15 grams of NaCl. In addition, we take in varying amounts of other electrolytes, including K⁺, H⁺, Ca²⁺, HCO₃⁻, and phosphate ions (HPO₄²⁻). The body’s task is to maintain mass balance: what comes in must be excreted if the body does not need it.

The body has several routes for excreting ions and water. The kidneys are the primary route for water loss and for removal of many ions. Under normal conditions, small amounts of both water and ions are lost in the feces and sweat as well. In addition, the lungs lose water and help remove H⁺ and HCO₃⁻ by excreting CO₂.

**RUNNING PROBLEM**

**Hyponatremia**

Lauren was competing in her first ironman distance triathlon, a 140.6-mile race consisting of 2.4 miles of swimming, 112 miles of cycling, and 26.2 miles of running. At mile 22 of the run, approximately 16 hours after starting the race, she collapsed. After being admitted to the medical tent, Lauren complained of nausea, a headache, and general fatigue. The medical staff noted that Lauren’s face and clothing were covered in white crystals. When they weighed her and compared that value with her pre-race weight recorded at registration, they realized Lauren had gained 2 kg during the race.

Although physiological mechanisms that maintain fluid and electrolyte balance are important, behavioral mechanisms also play an essential role. *Thirst* is critical because drinking is the only normal way to replace lost water. *Salt appetite* is a behavior that leads people and animals to seek and ingest salt (sodium chloride, NaCl).

Why are we concerned with homeostasis of these substances? Water and Na⁺ are associated with extracellular fluid volume and osmolarity. Disturbances in K⁺ balance can cause serious problems with cardiac and muscle function by disrupting the membrane potential of excitable cells. Ca²⁺ is involved in a variety of body processes, from exocytosis and muscle contraction to bone formation and blood clotting, and H⁺ and HCO₃⁻ are the ions whose balance determines body pH.

**ECF Osmolarity Affects Cell Volume**

Why is maintaining osmolarity so important to the body? The answer lies in the fact that water crosses most cell membranes freely. If the osmolarity of the extracellular fluid changes, water moves into or out of cells and changes intracellular volume. If ECF osmolarity decreases as a result of excess water intake, water moves into the cells and they swell. If ECF osmolarity increases as a result of salt intake, water moves out of the cells and they shrink. Cell volume is so important that many cells have independent mechanisms for maintaining it.

For example, renal tubule cells in the medulla of the kidney are constantly exposed to high extracellular fluid osmolarity, yet these cells maintain normal cell volume. They do so by synthesizing organic solutes as needed to make their intracellular osmolarity match that of the medullary interstitial fluid. The organic solutes used to raise intracellular osmolarity include sugar alcohols and certain amino acids. Other cells in the body regulate their volume by changing their ionic composition.

In a few instances, changes in cell volume are believed to act as signals that initiate certain cellular responses. For example, swelling of liver cells activates protein and glycogen synthesis, and shrinkage of these cells causes protein and glycogen breakdown. In many cases, however, inappropriate changes in cell volume—either shrinking or swelling—impair cell function. The brain, encased in the rigid skull, is particularly vulnerable to damage from swelling. In general, maintenance of ECF osmolarity within a normal range is essential to maintain cell volume homeostasis.

**Multiple Systems Integrate Fluid and Electrolyte Balance**

The process of fluid and electrolyte balance is truly integrative because it involves the respiratory and cardiovascular systems in addition to renal and behavioral responses. Adjustments made by the lungs and cardiovascular system are primarily under
neural control and can be made quite rapidly. Homeostatic compensation by the kidneys occurs more slowly because the kidneys are primarily under endocrine and neuroendocrine control. For example, small changes in blood pressure that result from increases or decreases in blood volume are quickly corrected by the cardiovascular control center in the brain. If volume changes are persistent or of large magnitude, the kidneys step in to help maintain homeostasis.

Figure 20.1 summarizes the integrated response of the body to changes in blood volume and blood pressure. Signals from carotid and aortic baroreceptors and atrial volume receptors initiate a quick neural response mediated through the cardiovascular control center and a slower response elicited from the kidneys. In addition, low blood pressure stimulates thirst. In both situations, renal function integrates with the cardiovascular system to keep blood pressure within a normal range.

Because of the overlap in their functions, a change made by one system—whether renal or cardiovascular—is likely to have consequences that affect the other. Endocrine pathways initiated by the kidneys have direct effects on the cardiovascular system, for instance, and hormones released by myocardial cells act on the kidneys. Sympathetic pathways from the cardiovascular control center affect not only cardiac output and vasoconstriction but also glomerular filtration and hormone release by the kidneys.

In this way the maintenance of blood pressure, blood volume, and ECF osmolarity forms a network of interwoven control pathways. This integration of function in multiple systems is one of the more difficult concepts in physiology, but it is also one of the most exciting areas of medicine and physiological research.

**Water Balance**

Water is the most abundant molecule in the body, constituting about 50% of total body weight in females ages 17 to 39, and 60% of total body weight in males of the same age group.
A 60-kg (132-lb) woman contains about 30 liters of body water, and the “standard” 70-kg man contains about 42 liters. Two-thirds of his water (about 28 liters) is inside the cells, about 3 liters are in the plasma, and the remaining 11 liters are in the interstitial fluid.

**Daily Water Intake and Excretion Are Balanced**

To maintain a constant volume of water in the body, we must take in the same amount of water that we excrete: intake must equal output. There are multiple avenues for daily water gain and loss (Fig. 20.2). On average, an adult ingests a little more than 2 liters of water in food and drink in a day. Normal metabolism, especially aerobic respiration (glucose + O\(_2\) → CO\(_2\) + H\(_2\)O), adds about 0.3 liter of water, bringing the total daily intake to approximately 2.5 liters.

Notice that the only means by which water normally enters the body from the external environment is by absorption through the digestive tract. Unlike some animals, we cannot absorb significant amounts of water directly through our skin. If fluids must be rapidly replaced or an individual is unable to eat and drink, fluid can be added directly to the plasma by means of intravenous (IV) injection, a medical procedure.

Most water is lost from the body in the urine, which has a daily volume of about 1.5 liters (Fig. 20.2). A small volume of water (about 100 mL) is lost in the feces. Additionally, water leaves the body through insensible water loss. This water loss, called insensible because we are not normally aware of it, occurs across the skin surface and through exhalation of humidified air. Even though the human epidermis is modified with an outer layer of keratin to reduce evaporative water loss in a terrestrial environment, we still lose about 900 mL of water insensibly each day. Thus the 2.5 liters of water we take in are balanced by the 2.5 liters that leave the body. Only water loss in the urine can be regulated.

Although urine is normally the major route of water loss, in certain situations other routes of water loss can become significant. Excessive sweating is one example. Another way in which water is lost is through diarrhea, a condition that can pose a major threat to the maintenance of water balance, particularly in infants.

Pathological water loss disrupts homeostasis in two ways. Volume depletion of the extracellular compartment decreases blood pressure. If blood pressure cannot be maintained through homeostatic compensations, the tissues do not get adequate oxygen. Also, if the fluid lost is hyposmotic to the body (as is the case in excessive sweating), the solutes left behind in the body raise osmolarity, potentially disrupting cell function.

Normally, water balance takes place automatically. Salty food makes us thirsty. Drinking 42 ounces of a soft drink means an extra trip to the bathroom. Salt and water balance is a subtle process that we are only peripherally aware of, like breathing and the beating of the heart.

Now that we have discussed why regulation of osmolarity is important, let’s see how the body accomplishes that goal.

**The Kidneys Conserve Water**

Figure 20.3 summarizes the role of the kidneys in water balance. The bottom line is that the kidneys can remove excess fluid by excreting it in the urine, but the kidneys cannot replace lost...
The Renal Medulla Creates Concentrated Urine

The concentration, or osmolarity, of urine is a measure of how much water is excreted by the kidneys. When maintenance of homeostasis requires eliminating excess water, the kidneys produce copious amounts of dilute urine with an osmolarity as low as 50 mOsM. Removal of excess water in urine is known as diuresis (diourein, to pass in urine). Drugs that promote the excretion of urine are called diuretics. In contrast, if the kidneys need to conserve water, the urine becomes quite concentrated. Specialized mechanisms in the medulla of the kidney allow urine to be up to four times as concentrated as the blood (1200 mOsM versus the blood’s 300 mOsM).

The kidneys control urine concentration by varying the amounts of water and Na+ reabsorbed in the distal nephron (distal tubule and collecting duct). To produce dilute urine, the kidney must reabsorb solute without allowing water to follow by osmosis. This means that the apical tubule cell membranes must not be permeable to water. On the other hand, if urine is to become concentrated, the nephron must be able to reabsorb water but leave solute in the tubule lumen.

Mechanistically, it seems simple enough to create an epithelium that transports solutes but is impermeable to water (dilute urine)—simply remove all water pores on the apical cell membrane. But mechanistically it seems much more difficult to create concentrated urine. How can the kidney reabsorb water without first reabsorbing solute? At one time, scientists speculated that water was actively transported on carriers, just as Na+ and other ions are. However, once scientists developed micropuncture techniques for sampling fluid inside kidney tubules, they discovered that water is reabsorbed only by osmosis through water pores (aquaporins).

The mechanism for absorbing water without solute turned out to be simple: make the collecting duct cells and interstitial fluid surrounding them more concentrated than the fluid flowing into the tubule. Then, if the tubule cells have water pores, water can be absorbed from the lumen without first reabsorbing solute. This is indeed the situation in the kidney. Through an unusual arrangement of blood vessels and renal tubules, which we discuss later, the renal medulla maintains a high osmotic concentration in its cells and interstitial fluid. This high medullary interstitial osmolarity allows urine to be concentrated as it flows through the collecting duct.

Let’s follow some filtered fluid through a nephron to see where these changes in osmolarity take place (Fig. 20.4). The renal cortex has an interstitial osmolarity of about 300 mOsM. Reabsorption in the proximal tubule is isosmotic, and filtrate entering the loop of Henle has an osmolarity of about 300 mOsM (Fig. 20.4 1).

As the nephrons dip into the medulla, the interstitial osmolarity steadily increases until it reaches about 1200 mOsM where the collecting ducts empty into the renal pelvis. Fluid passing through the descending limb of the loop...
Integrative Physiology II: Fluid and Electrolyte Balance

loses water to the interstitium. Tubule fluid at the bottom of the loop will be of the same osmolarity as in the medulla.

In the ascending limb, the permeability of the tubule wall changes. The cells in the thick portion of the ascending limb of the loop have apical surfaces (facing the tubule lumen) that are impermeable to water. These cells do transport ions out of the tubule lumen (Fig. 20.4 2), but in this part of the nephron, solute movement is not followed by water movement. The reabsorption of solute without water decreases the concentration of the tubule fluid. Fluid leaving the loop of Henle therefore is hyposmotic, with an osmolarity of around 100 mOsM. The loop of Henle is the primary site where the kidney creates hyposmotic fluid.

Once hyposmotic fluid leaves the loop of Henle, it passes into the distal nephron. Here the water permeability of the tubule cells is variable and under hormonal control (Fig. 20.4 3). When the apical membrane of distal nephron cells is not permeable to water, water cannot leave the tubule, and the filtrate remains dilute. A small amount of additional solute can be reabsorbed as fluid passes along the collecting duct, making the filtrate even more dilute. When this happens, the concentration of urine can be as low as 50 mOsM (Fig. 20.4 4).

### OSMOLARITY CHANGES THROUGH THE NEPHRON

1. Iosmotic fluid leaving the proximal tubule becomes progressively more concentrated in the descending limb.
2. Removal of solute in the thick ascending limb creates hyposmotic fluid.
3. Permeability to water and solutes is regulated by hormones.
4. Urine osmolarity depends on reabsorption in the collecting duct.

#### CLINICAL FOCUS: DIABETES

**Osmotic Diuresis**

The primary sign of diabetes mellitus is an elevated blood glucose concentration. In untreated diabetics, if blood glucose levels exceed the renal threshold for glucose reabsorption, glucose is excreted in the urine. This may not seem like a big deal, but any additional solute that remains in the lumen forces additional water to be excreted, causing osmotic diuresis. Suppose, for example, that the nephrons must excrete 300 milliosmoles of NaCl. If the urine is maximally concentrated at 1200 mOsM, the NaCl is excreted in a volume of 0.25 L. However, if the NaCl is joined by 300 milliosmoles of glucose that must be excreted, the volume of urine doubles, to 0.5 L. Osmotic diuresis in untreated diabetics (primarily type 1) causes polyuria (excessive urination) and polydipsia (excessive thirst) (dipsos, thirsty) as a result of dehydration and high plasma osmolarity.
On the other hand, if the body needs to conserve water by reabsorbing it, the tubule epithelium in the distal nephron must become permeable to water. Under hormonal control, the cells insert water pores into their apical membranes. Once water can enter the epithelial cells, osmosis draws water out of the less-concentrated lumen and into the more concentrated interstitial fluid. At maximal water permeability, removal of water from the tubule leaves behind concentrated urine with an osmolarity that can be as high as 1200 mOsM (Fig. 20.4).

Water reabsorption in the kidneys conserves water and can decrease body osmolarity to some degree when coupled with excretion of solute in the urine. But remember that the kidney’s homeostatic mechanisms can do nothing to restore lost fluid volume. Only the ingestion or infusion of water can replace water that has been lost.

### Vasopressin Controls Water Reabsorption

How do the distal tubule and collecting duct cells alter their permeability to water? The process involves adding or removing water pores in the apical membrane under the direction of the posterior pituitary hormone vasopressin. In most mammals, the nine-amino-acid peptide contains the amino acid arginine, so vasopressin is called arginine vasopressin or AVP. Because vasopressin causes the body to retain water, it is also known as antidiuretic hormone (ADH).

When vasopressin acts on target cells, the collecting duct epithelium becomes permeable to water, allowing water to move out of the lumen (Fig. 20.5a). The water moves by osmosis because solute concentration in the cells and interstitial fluid of the renal medulla is higher than that of fluid in the tubule. In the absence of vasopressin, the collecting duct is impermeable to water (Fig. 20.5b). Although a concentration gradient is present across the epithelium, water remains in the tubule, producing dilute urine.

The water permeability of the collecting duct is not an all-or-none phenomenon, as the previous paragraph might suggest. Permeability is variable, depending on how much vasopressin is present. The graded effect of vasopressin allows the body to match urine concentration closely to the body’s needs.

### Vasopressin and Aquaporins

Most membranes in the body are freely permeable to water. What makes the cells of the distal nephron different? The answer lies with the water pores found in these cells. Water pores are aquaporins, a family of membrane channels with at least 10 different isoforms that occur in mammalian tissues. The kidney has multiple isoforms of aquaporins, including aquaporin-2 (AQP2), the water channel regulated by vasopressin.

AQP2 in a collecting duct cell may be found in two locations: on the apical membrane facing the tubule lumen and in the membrane of cytoplasmic storage vesicles (Fig. 20.5c). (Two other isoforms of aquaporins are present in the basolateral membrane, but they are not regulated by vasopressin.) When vasopressin levels and, consequently, collecting duct water permeability are low, the collecting duct cell has few water pores in its apical membrane and stores its AQP2 water pores in cytoplasmic storage vesicles.

When vasopressin arrives at the collecting duct, it binds to its V2 receptors on the basolateral side of the cell (step 1 in Fig. 20.5c). Binding activates a G-protein/cAMP second messenger system. Subsequent phosphorylation of intracellular proteins causes the AQP2 vesicles to move to the apical membrane and fuse with it. Exocytosis inserts the AQP2 water pores into the apical membrane. Now the cell is permeable to water. This process, in which parts of the cell membrane are alternately added by exocytosis and withdrawn by endocytosis, is known as membrane recycling.

### Concept Check

1. Does the apical membrane of a collecting duct cell have more water pores when vasopressin is present or when it is absent?

### Blood Volume and Osmolarity

#### Activate Osmoreceptors

What stimuli control vasopressin secretion? There are three: plasma osmolarity, blood volume, and blood pressure (Fig. 20.6). The most potent stimulus for vasopressin release is an increase in plasma osmolarity. Osmolarity is monitored by osmoreceptors, stretch-sensitive neurons that increase their firing rate as osmolarity increases. Our current model indicates that when the osmoreceptors shrink, cation channels linked to actin filaments open, depolarizing the cell.

The primary osmoreceptors for vasopressin release are in the hypothalamus. When plasma osmolarity is below the threshold value of 280 mOsM, the osmoreceptors do not fire, and vasopressin release from the pituitary ceases (Fig. 20.6b). If plasma osmolarity rises above 280 mOsM, the osmoreceptors stimulate release of vasopressin.

Decreases in blood pressure and blood volume are less powerful stimuli for vasopressin release. The primary receptors for decreased volume are stretch-sensitive receptors in the atria. Blood pressure is monitored by the same carotid and aortic baroreceptors that initiate cardiovascular responses. When blood pressure or blood volume is low, these receptors signal the hypothalamus to secrete vasopressin and conserve fluid.

In adults, vasopressin secretion also shows a circadian rhythm, with increased secretion during the overnight hours. As a result of this increase, less urine is produced overnight than during the day, and the first urine excreted in the morning is more concentrated. One theory for the cause of bed-wetting, or
**Vasopressin makes the collecting duct permeable to water.**

(a) With maximal vasopressin, the collecting duct is freely permeable to water. Water leaves by osmosis and is carried away by the vasa recta capillaries. Urine is concentrated.

(b) In the absence of vasopressin, the collecting duct is impermeable to water and the urine is dilute.

(c) Vasopressin causes insertion of water pores into the apical membrane.

**Fig. 20.5**
Vasopressin

High osmolarity or low blood pressure cause vasopressin release.

(a) Control of vasopressin secretion

- Decreased blood pressure
- Decreased atrial stretch due to low blood volume
- Osmolarity greater than 280 mOsm

- Carotid and aortic baroreceptors
- Atrial stretch receptor
- Hypothalamic osmoreceptors

- Sensory neuron to hypothalamus
- Sensory neuron to hypothalamus
- Interneurons to hypothalamus

- Hypothalamic neurons that synthesize vasopressin

- Vasopressin (released from posterior pituitary)

- Collecting duct epithelium
- Insertion of water pores in apical membrane
- Increased water reabsorption to conserve water

(b) The effect of plasma osmolarity on vasopressin secretion

ARGinine VASOPRESSin (AVP), Antidiuretic hormone (ADH)

- Origin: Hypothalamic neurons. Released from posterior pituitary
- Chemical nature: 9-amino acid peptide
- Transport in the circulation: Dissolved in plasma
- Half-life: 15 min
- Factors affecting release: ↑ Osmolarity (hypothalamic osmoreceptors) ↓ Blood pressure or volume (carotid, aortic, atrial receptors)
- Target cells or tissues: Renal collecting duct
- Receptor/second messenger: V2 receptor/cAMP
- Tissue action: Increases renal water reabsorption
- Action at cellular-molecular level: Inserts AQP water pores in apical membrane

FIGURE QUESTIONS
1. What is the threshold osmolarity for vasopressin release?
2. What signal in the AVP neuron triggers exocytosis of AVP-containing vesicles?
**Overview of the Countercurrent Exchange**

The descending limb is integrative physiology II: fluid and electrolyte balance. It is a descending limb that forms a high surface-area-to-volume ratio. Without a heat exchanger, warm blood flowing from the body core into the limb would easily lose heat to the surrounding environment (Fig. 20.7a). With a countercurrent heat exchanger, warm arterial blood entering the limb transfers its heat to cooler venous blood flowing from the tip of the limb back into the body (Fig. 20.7b). This arrangement reduces the amount of heat lost to the external environment.

The countercurrent exchange system of the kidney works on the same principle, except that it transfers water and solutes instead of heat. However, because the kidney forms a closed system, the solutes are not lost to the environment. Instead, the solutes concentrate in the interstitium. This process is aided by active transport of solutes out of the ascending limb of the loop of Henle, which makes the ECF osmolarity even greater.

A countercurrent exchange system in which exchange is enhanced by active transport of solutes is called a countercurrent multiplier.

**The Loop of Henle Is a Countercurrent Multiplier**

Vasopressin is the signal for water reabsorption out of the nephron tubule, but the key to the kidney’s ability to produce concentrated urine is the high osmolarity of the medullary interstitium (interstitial fluid compartment of the kidney). Without it, there would be no concentration gradient for osmotic movement of water out of the collecting duct. What creates this high ECF osmolarity? And why isn’t the interstitial fluid osmolarity reduced as water is reabsorbed from the collecting duct and descending limb of the loop of Henle (see Fig. 20.4)?

The answers to these questions lie in the anatomical arrangement of the loop of Henle and its associated blood vessels, the vasa recta. Together, these structures form a countercurrent exchange system.

**Countercurrent Exchange Systems**

Countercurrent exchange systems require arterial and venous blood vessels that pass very close to each other, with their fluid flow moving in opposite directions (the name countercurrent reflects the fact that the two flows run counter to each other). This anatomical arrangement allows the passive transfer of heat or molecules from one vessel to the other. Because the countercurrent heat exchanger is easier to understand, we first examine how it works and then apply the same principle to the kidney.

The countercurrent heat exchanger in mammals and birds evolved to reduce heat loss from flippers, tails, and other limbs that are poorly insulated and have a high surface-area-to-volume ratio. Without a heat exchanger, warm blood flowing from the body core into the limb would easily lose heat to the surrounding environment (Fig. 20.7a). With a countercurrent heat exchanger, warm arterial blood entering the limb transfers its heat to cooler venous blood flowing from the tip of the limb back into the body (Fig. 20.7b). This arrangement reduces the amount of heat lost to the external environment.

The countercurrent exchange system of the kidney works on the same principle, except that it transfers water and solutes instead of heat. However, because the kidney forms a closed system, the solutes are not lost to the environment. Instead, the solutes concentrate in the interstitium. This process is aided by active transport of solutes out of the ascending limb of the loop of Henle, which makes the ECF osmolarity even greater. A countercurrent exchange system in which exchange is enhanced by active transport of solutes is called a countercurrent multiplier.

**The Renal Countercurrent Multiplier**

An overview of the countercurrent multiplier system in the renal medulla is shown in Figure 20.7c. The system has two components: loops of Henle that leave the cortex, dip down into the more concentrated environment of the medulla, then ascend into the cortex again, and the peritubular capillaries known as the vasa recta. These capillaries, like the loop of Henle, dip down into the medulla and then go back up to the cortex, also forming hairpin loops that act as a countercurrent exchanger.

Although textbooks traditionally show a single nephron with a single loop of capillary (as we do in Fig. 20.7c), each kidney has thousands of collecting ducts and loops of Henle packed between thousands of vasa recta capillaries, blurring the direct association between a nephron and its vascular supply. Functionally, blood flow in the vasa recta moves in the opposite direction from filtrate flow in the loops of Henle, as shown in Figure 20.7c.

Let’s follow some fluid as it moves through the loop. Isosmotic filtrate from the proximal tubule first flows into the descending limb of the loop of Henle. The descending limb is permeable to water but does not transport ions. As the loop dips into the medulla, water moves by osmosis from the descending limb into the progressively more concentrated interstitial fluid, leaving solutes behind in the tubule lumen.

The filtrate becomes progressively more concentrated as it moves deeper into the medulla. At the tips of the longest loops of Henle, the filtrate reaches a concentration of 1200 mOsM. Filtrate in shorter loops (which do not extend into the most concentrated regions of the medulla) does not reach such a high concentration.

When the fluid flow reverses direction and enters the ascending limb of the loop, the properties of the tubule epithelium change. The tubule epithelium in this segment of the nephron is impermeable to water while actively transporting Na⁺, K⁺, and other ions.
**COUNTERCURRENT MECHANISMS**

**A countercurrent heat exchanger**

(a) If blood vessels are not close to each other, heat is dissipated to the external environment.

(b) Countercurrent heat exchanger allows warm blood entering the limb to transfer heat directly to blood flowing back into the body.

(c) Countercurrent exchange in the vasa recta

Filtrate entering the descending limb becomes progressively more concentrated as it loses water.

Dilute filtrate in the lumen.

The ascending limb pumps out Na⁺, K⁺, and Cl⁻, and filtrate becomes hyposmotic.

(d) The apical surface of the ascending limb is not permeable to water. Active reabsorption of ions in this region creates a dilute filtrate in the lumen.

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**KEY**

- **H₂O** = ○
- **K⁺** = ★
- **Cl⁻** = ●
- **Na⁺** = ▲

---

**Fig. 20.7**
and Cl\(^-\) out of the tubule into the interstitial fluid. The loss of solute from the lumen causes the filtrate osmolarity to decrease steadily, from 1200 mOsM at the bottom of the loop to 100 mOsM at the point where the ascending limb leaves the medulla and enters the cortex. The net result of the countercurrent multiplier in the kidney is to produce hyperosmotic interstitial fluid in the medulla and hyposmotic filtrate leaving the loop of Henle.

Normally, about 25% of all Na\(^+\) and K\(^+\) reabsorption takes place in the ascending limb of the loop. Some transporters responsible for active ion reabsorption in the thick portion of the ascending limb are shown in Figure 20.7d. The NKCC \textit{symporter} uses energy stored in the Na\(^+\) concentration gradient to transport Na\(^+\), K\(^+\), and 2 Cl\(^-\) from the lumen into the epithelial cells of the ascending limb. The Na\(^+\)-K\(^+\)-ATPase removes Na\(^+\) from the cells on the basolateral side of the epithelium, while K\(^+\) and Cl\(^-\) leave the cells together on a cotransport protein or through open channels. NKCC-mediated transport can be inhibited by drugs known as "loop diuretics," such as \textit{furosemide} (Lasix).

**Concept Check**

6. Explain why patients taking a loop diuretic that inhibits solute reabsorption excrete greater-than-normal volumes of urine.

7. Loop diuretics that inhibit the NKCC \textit{symporter} are sometimes called "potassium-wasting" diuretics. Explain why people who are on loop diuretics must increase their dietary K\(^+\) intake.

**The Vasa Recta Removes Water** It is easy to see how transport of solute out of the ascending limb of the loop of Henle dilutes the filtrate and helps concentrate the interstitial fluid in the medulla. Still, why doesn’t the water leaving the descending limb of the loop (see Fig. 20.7c) dilute the interstitial fluid of the medulla? The answer lies in the close anatomical association of the loop of Henle and the peritubular capillaries of the vasa recta, which functions as a countercurrent exchanger.

Water or solutes that leave the tubule move into the vasa recta if an osmotic or concentration gradient exists between the medullary interstitium and the blood in the vasa recta. For example, assume that at the point at which the vasa recta enters the medulla, the blood in the vasa recta is 300 mOsM, isosmotic with the cortex. As the blood flows deeper into the medulla, it loses water and picks up solutes transported out of the ascending limb of the loop of Henle, carrying these solutes farther into the medulla. By the time the blood reaches the bottom of the vasa recta loop, it has a high osmolarity, similar to that of the surrounding interstitial fluid (1200 mOsM).

Then, as blood in the vasa recta flows back toward the cortex, the high plasma osmolarity attracts the water that is being lost from the descending limb, as Figure 20.7c shows. The movement of this water into the vasa recta decreases the osmolarity of the blood while simultaneously preventing the water from diluting the concentrated medullary interstitial fluid.

The end result of this arrangement is that blood flowing through the vasa recta removes the water reabsorbed from the loop of Henle. Without the vasa recta, water moving out of the descending limb of the loop of Henle would eventually dilute the medullary interstitium. The vasa recta thus plays an important part in keeping the medullary solute concentration high.

**Urea Increases the Osmolarity of the Medullary Interstitium** The high solute concentration in the medullary interstitium is only partly due to NaCl. Nearly half the solute in this compartment is urea. Where does this urea come from? For many years scientists thought urea crossed cell membranes only by passive transport. However, in recent years researchers have learned that membrane transporters for urea are present in the collecting duct and loops of Henle. One family of transporters consists of facilitated diffusion carriers, and the other family has Na\(^+\)-dependent secondary active transporters. These urea transporters help concentrate urea in the medullary interstitium, where it contributes to the high interstitial osmolarity.

**Sodium Balance and ECF Volume** With an average American diet, we ingest a lot of NaCl—about 9 grams per day. This is about 2 teaspoons of salt, or 155 millimoles of Na\(^+\) and 155 millimoles of Cl\(^-\). Let’s see what would happen to our bodies if the kidneys could not get rid of this Na\(^+\).

Our normal plasma Na\(^+\) concentration, measured from a venous blood sample, is 135–145 millimoles Na\(^+\) per liter of plasma. Because Na\(^+\) distributes freely between plasma and interstitial fluid, this value also represents our ECF Na\(^+\) concentration. If we add 155 millimoles of Na\(^+\) to the ECF, how much water would we have to add to keep the ECF Na\(^+\) concentration at 140 mOsM? One form of an equation asking this question is

\[ 155 \text{ mosmol} / x \text{ liters} = 140 \text{ mosmol/liter} \]

\[ x = 1.1 \text{ liters} \]

We would have to add more than a liter of water to the ECF to compensate for the addition of the Na\(^+\). Normal ECF volume is about 14 liters, and so that increase in volume would represent about an 8% gain! Imagine what that volume increase would do to blood pressure.

Suppose, however, that instead of adding water to keep plasma concentrations constant, we add the NaCl but don’t drink any water. What happens to osmolarity now? If we assume that normal total body osmolarity is 300 mOsM and that the volume of fluid in the body is 42 L, the addition of 155 millimoles of Na\(^+\) and 155 millimoles of Cl\(^-\) would increase total body osmolarity to 307 mOsM—a substantial increase.

\* \((155 \text{ mosmol Na}^+ + 155 \text{ mosmol Cl}^-) / 42 \text{ L} = 7.4 \text{ mosmol/L added;}
300 \text{ mosmol/L initial} + 7.4 \text{ mosmol/L added} = 307 \text{ mOsM final} \)
In addition, because NaCl is a nonpenetrating solute, it would stay in the ECF. Higher osmolarity in the ECF would draw water from the cells, shrinking them and disrupting normal cell function.

Fortunately, our homeostatic mechanisms usually maintain mass balance: anything extra that comes into the body is excreted. Figure 20.8 shows a generalized homeostatic pathway for sodium balance in response to salt ingestion. Here’s how it works:

The addition of NaCl to the body raises osmolarity. This stimulus triggers two responses: vasopressin secretion and thirst. Vasopressin release causes the kidneys to conserve water (by reabsorbing water from the filtrate) and concentrate the urine. Thirst prompts us to drink water or other fluids. The increased fluid intake decreases osmolarity, but the combination of salt and water intake increases both ECF volume and blood pressure. These increases then trigger another series of control pathways, which bring ECF volume, blood pressure, and total-body osmolality back into the normal range by excreting extra salt and water.

The kidneys are responsible for most Na⁺ excretion, and normally only a small amount of Na⁺ leaves the body in feces and perspiration. However, in situations such as vomiting, diarrhea, and heavy sweating, we may lose significant amounts of Na⁺ and Cl⁻ through nonrenal routes.

Although we speak of ingesting and losing salt (NaCl), only renal Na⁺ absorption is regulated. And actually, the stimuli that set the Na⁺ balance pathway in motion are more closely tied to blood volume and blood pressure than to Na⁺ levels. Chloride movement usually follows Na⁺ movement, either indirectly via the electrochemical gradient created by Na⁺ transport or directly via membrane transporters such as the NKCC transporter of the loop of Henle or the Na⁺-Cl⁻ symporter of the distal tubule.

**Aldosterone Controls Sodium Balance**

The regulation of blood Na⁺ levels takes place through one of the most complicated endocrine pathways of the body. The reabsorption of Na⁺ in the distal tubules and collecting ducts of the kidney is regulated by the steroid hormone aldosterone: the more aldosterone, the more Na⁺ reabsorption. Because one target of aldosterone is increased activity of the Na⁺-K⁺-ATPase, aldosterone also causes K⁺ secretion (Fig. 20.9).

Aldosterone is a steroid hormone synthesized in the adrenal cortex, the outer portion of the adrenal gland that sits atop each kidney. Like other steroid hormones, aldosterone is secreted into the blood and transported on a protein carrier to its target.

The primary site of aldosterone action is the last third of the distal tubule and the portion of the collecting duct that runs through the kidney cortex (the cortical collecting duct). The primary target of aldosterone is principal cells, or P cells (Fig. 20.9b). Principal cells are arranged much like other polarized transporting epithelial cells, with Na⁺-K⁺-ATPase pumps on the basolateral membrane, and various channels and transporters on the apical membrane. In principal cells, the apical membranes contain leak channels for Na⁺ (called ENaC, for epithelial Na⁺ channel) and for K⁺ (called ROMK, for renal outer medulla K⁺ channel).

Aldosterone enters P cells by simple diffusion. Once inside, it combines with a cytoplasmic receptor (Fig. 20.9b). In the early response phase, apical Na⁺ and K⁺ channels increase their open time under the influence of an as-yet-unidentified signal molecule. As intracellular Na⁺ levels rise, the Na⁺-K⁺-ATPase pump speeds up, transporting cytoplasmic Na⁺ into the ECF and bringing K⁺ from the ECF into the P cell. The net result is a rapid increase in Na⁺ reabsorption and K⁺ secretion that does not require the synthesis of new channel or ATPase proteins. In the slower phase of aldosterone action, newly synthesized channels and pumps are inserted into epithelial cell membranes (Fig. 20.9b).
Aldosterone

(a) The primary action of aldosterone is renal sodium reabsorption.

(b) Aldosterone acts on principal cells.
Note that Na\(^+\) and water reabsorption are separately regulated in the distal nephron. Water does not automatically follow Na\(^+\) reabsorption: vasopressin must be present to make the distal-nephron epithelium permeable to water. In contrast, Na\(^+\) reabsorption in the proximal tubule is automatically followed by water reabsorption because the proximal tubule epithelium is always freely permeable to water.

**Low Blood Pressure Stimulates Aldosterone Secretion**

What controls physiological aldosterone secretion from the adrenal cortex? There are two primary stimuli: increased extracellular K\(^+\) concentration and decreased blood pressure (Fig. 20.9a). Elevated K\(^+\) concentrations act directly on the adrenal cortex in a reflex that protects the body from hyperkalemia. Decreased blood pressure initiates a complex pathway that results in release of a hormone, angiotensin II, that stimulates aldosterone secretion in most situations.

Two additional factors modulate aldosterone release in pathological states: an increase in ECF osmolarity acts directly on adrenal cortex cells to inhibit aldosterone secretion during dehydration, and an abnormally large (10–20 mEq/L) decrease in plasma Na\(^+\) can directly stimulate aldosterone secretion.

**The Renin-Angiotensin Pathway** Angiotensin II (ANG II) is the usual signal controlling aldosterone release from the adrenal cortex. ANG II is one component of the renin-angiotensin system (RAS), a complex, multistep pathway for maintaining blood pressure. The RAS pathway begins when juxtaglomerular granular cells in the afferent arterioles of a nephron secrete an enzyme called renin (Fig. 20.10). Renin converts an inactive plasma protein, angiotensinogen, into angiotensin I (ANG I). (The suffix -ogen indicates an inactive precursor.) When ANG I in the blood encounters an enzyme called angiotensin-converting enzyme (ACE), ANG I is converted into ANG II.

This conversion was originally thought to take place only in the lungs, but ACE is now known to occur on the endothelium of blood vessels throughout the body. When ANG II in the blood reaches the adrenal gland, it causes synthesis and release of aldosterone. Finally, at the distal nephron, aldosterone initiates the intracellular reactions that cause the tubule to reabsorb Na\(^+\).

The stimuli that begin the RAS pathway are all related either directly or indirectly to low blood pressure (Fig. 20.10):

1. The granular cells are directly sensitive to blood pressure. They respond to low blood pressure in renal arterioles by secreting renin.
2. Sympathetic neurons, activated by the cardiovascular control center when blood pressure decreases, terminate on the granular cells and stimulate renin secretion.
3. Paracrine feedback—from the macula densa in the distal tubule to the granular cells—stimulates renin release. When fluid flow through the distal tubule is relatively high, the macula densa cells release paracervines, which inhibit renin release. When fluid flow in the distal tubule decreases, macula densa cells signal the granular cells to secrete renin.

Sodium reabsorption does not directly raise low blood pressure, but retention of Na\(^+\) increases osmolarity, which stimulates thirst. Fluid intake when the person drinks more water increases ECF volume (see Fig. 20.8). When blood volume increases, blood pressure also increases.

The effects of the RAS pathway are not limited to aldosterone release, however. Angiotensin II is a remarkable hormone with additional effects directed at raising blood pressure. These actions make ANG II an important hormone in its own right, not merely an intermediate step in the aldosterone control pathway.

**ANG II Has Many Effects**

Angiotensin II has significant effects on fluid balance and blood pressure beyond stimulating aldosterone secretion, underscoring the integrated functions of the renal and cardiovascular systems. ANG II increases blood pressure both directly and indirectly through four additional pathways (Fig. 20.10):

1. ANG II increases vasopressin secretion. ANG II receptors in the hypothalamus initiate this reflex. Fluid retention in the kidney under the influence of vasopressin helps conserve blood volume, thereby maintaining blood pressure.
2. ANG II stimulates thirst. Fluid ingestion is a behavioral response that expands blood volume and raises blood pressure.
3. ANG II is one of the most potent vasoconstrictors known in humans. Vasoconstriction causes blood pressure to increase without a change in blood volume.
4. Activation of ANG II receptors in the cardiovascular control center increases sympathetic output to the heart and blood vessels. Sympathetic stimulation increases cardiac output and vasoconstriction, both of which increase blood pressure.
5. ANG II increases proximal tubule Na\(^+\) reabsorption. ANG II stimulates an apical transporter, the Na\(^+\)-H\(^+\) exchanger (NHE). Sodium reabsorption in the proximal tubule is followed by water reabsorption, so the net effect is reabsorption of isosmotic fluid, conserving volume.
The Renin-angiotensin System (RAS)

This map outlines the control of aldosterone secretion as well as the blood pressure–raising effects of ANG II. The pathway begins when decreased blood pressure stimulates renin secretion.

**ANGIOTENSIN (ANG II)**

- **Origin**: Inactive precursor protein angiotensinogen made by liver
- **Chemical nature**: 8-amino-acid peptide
- **Biosynthesis**: Angiotensinogen \( \rightarrow \) ANG I \( \rightarrow \) ANG II
- **Transport in the circulation**: Dissolved in plasma
- **Half-life**: 1 min (renin half-life: 10–20 min)
- **Factors affecting release**: ↓ Blood pressure (via renin)
- **Control pathway**: Renin-angiotensin system
- **Target cells or tissues**: Adrenal cortex, arterioles, brain
- **Receptor**: AT receptors
- **Tissue action**: Adrenal cortex: secrete aldosterone
  Arterioles: vasoconstrict
  Medulla oblongata: reflexes to increase blood pressure
  Hypothalamus: vasopressin secretion and increased thirst

**FIGURE QUESTION**

Add efferent pathways and/or targets to the pathways marked with a "•".
Once these blood pressure–raising effects of ANG II became known, it was not surprising that pharmaceutical companies started looking for drugs to block ANG II. Their research produced a new class of antihypertensive drugs called ACE inhibitors. These drugs block the ACE-mediated conversion of ANG I to ANG II, thereby helping to relax blood vessels and lower blood pressure. Less ANG II also means less aldosterone release, a decrease in \( \text{Na}^+ \) reabsorption and, ultimately, a decrease in ECF volume. All these responses contribute to lowering blood pressure.

However, the ACE inhibitors have side effects in some patients. ACE inactivates a cytokine called bradykinin. When ACE is inhibited by drugs, bradykinin levels increase, and in some patients this creates a dry, hacking cough. One solution was the development of drugs called angiotensin receptor blockers (ARBs), which block the blood pressure–raising effects of ANG II at target cells by binding to \( \text{AT}_1 \) receptors. Recently another new class of drugs, direct renin inhibitors, was approved. Direct renin inhibitors decrease the plasma activity of renin, which in turn blocks production of ANG I and inhibits the entire RAS pathway.

### Concept Check

10. A man comes to the doctor with high blood pressure. Tests show that he also has elevated plasma renin levels and atherosclerotic plaques that have nearly blocked blood flow through his renal arteries. How does decreased blood flow in his renal arteries cause elevated renin levels?

11. Map the pathways through which elevated renin causes high blood pressure in the man mentioned in Concept Check 10.

12. Why is it more effective to put ACE in the pulmonary vasculature than in the systemic vasculature?

### ANP Promotes \( \text{Na}^+ \) and Water Excretion

Once it was known that aldosterone and vasopressin increase \( \text{Na}^+ \) and water reabsorption, scientists speculated that other hormones might cause \( \text{Na}^+ \) loss, or natriuresis (natrium, sodium + ourein, to urinate) and water loss (diuresis) in the urine. If found, these hormones might be used clinically to lower blood volume and blood pressure in patients with essential hypertension. During years of searching, however, evidence for the other hormones was not forthcoming.

Then, in 1981, a group of Canadian researchers found that injections of homogenized rat atria caused rapid but short-lived excretion of \( \text{Na}^+ \) and water in the rats’ urine. They hoped they had found the missing hormone, one whose activity would complement that of aldosterone and vasopressin. As it turned out, they had discovered the first natriuretic peptide (NP), one member of a family of hormones that appear to be endogenous RAS antagonists (Fig. 20.11).

Atrial natriuretic peptide (ANP; also known as atriopeptin) is a peptide hormone produced in specialized myocardial cells primarily in the atria of the heart. ANP is synthesized as part of a large prohormone that is cleaved into several active hormone fragments. A related hormone, brain natriuretic peptide (BNP), is synthesized by ventricular myocardial cells and certain brain neurons. Both natriuretic peptides are released by the heart when myocardial cells stretch more than normal. The natriuretic peptides bind to membrane receptor-enzymes that work through a cGMP second messenger system.

ANP is the more important signal molecule in normal physiology. ANP is released when increased blood volume causes increased atrial stretch. At the systemic level, ANP enhances \( \text{Na}^+ \) and water excretion to decrease blood volume. ANP acts at multiple sites. In the kidney it increases GFR by dilating the afferent arterioles, and it directly decreases \( \text{Na}^+ \) reabsorption in the collecting duct.

Natriuretic peptides also act indirectly to increase \( \text{Na}^+ \) and water excretion by suppressing the release of renin, aldosterone, and vasopressin (Fig. 20.11), actions that reinforce the natriuretic-diuretic effect. In addition, natriuretic peptides act directly on the cardiovascular control center of the medulla to lower blood pressure.

Brain natriuretic peptide (BNP) is now recognized as an important biological marker for heart failure because production of this substance increases with ventricular dilation and increased ventricular pressure. Hospital emergency departments now use BNP levels to distinguish dyspnea (difficulty breathing) in heart failure from other causes. BNP levels are also used as an independent predictor of heart failure and sudden death from cardiac arrhythmias.

### Running Problem

The medical staff analyzed Lauren’s blood for electrolyte concentrations. Her serum \( \text{Na}^+ \) concentration was 124 mEq/L. The normal range is 135–145 mEq/L. Lauren’s diagnosis was hyponatremia (hypo-, below + natri-, sodium + -emia, blood), defined as a serum \( \text{Na}^+ \) concentration below 135 mEq/L. Hyponatremia induced by the consumption of large quantities of low-sodium or sodium-free fluid, which is what happened in Lauren’s case, is sometimes called dilutional hyponatremia.

**Q3:** Which body fluid compartment is being diluted in dilutional hyponatremia?

**Q4:** One way to estimate body osmolarity is to double the plasma \( \text{Na}^+ \) concentration. Estimate Lauren’s osmolarity and explain what effect the dilutional hyponatremia has on her cells.

**Q5:** In dilutional hyponatremia, the medical personnel are most concerned about which organ or tissue?
Natriuretic Peptides

Atrial natriuretic peptide (ANP) promotes salt and water excretion. Brain natriuretic peptide (BNP) is a clinical marker for heart failure.

**NATRIURETIC PEPTIDES (ANP, BNP)**

- **Origin**: Myocardial cells
- **Chemical nature**: Peptides. ANP: 28 amino acids, BNP: 32 amino acids
- **Biosynthesis**: Typical peptide. Stored in secretory cells
- **Transport in the circulation**: Dissolved in plasma
- **Half-life**: ANP: 2–3 min, BNP: 12 min
- **Factors affecting release**: ↑ Myocardial stretch. ANP: atrial stretch due to increased blood volume. BNP: ventricular stretch in heart failure
- **Target cells or tissues**: ANP: kidney, brain, adrenal cortex primarily
- **Receptor**: NPR receptors. Guanylyl cyclase-linked receptor-enzymes
- **Systemic action of ANP**: Increase salt and water excretion
- **Tissue action**: Afferent arterioles: vasodilate to increase GFR; inhibit renin secretion
  - Nephron: decrease Na⁺ and water reabsorption
  - Adrenal cortex: inhibit aldosterone secretion
  - Medulla oblongata: reflexes to decrease blood pressure
  - Hypothalamus: inhibit vasopressin secretion

**Fig. 20.11 ESSENTIALS**

- Increased blood volume causes increased atrial stretch.
- Myocardial cells stretch and release.
- Natriuretic peptides
- Hypothalamus
- Kidney
  - Afferent arteriole
    - Dilates
    - ↓ Na⁺ reabsorption
    - ↑ NaCl and H₂O excretion
    - Decreased blood volume
- Tubule
- Adrenal cortex
  - Decreased sympathetic output
  - Less aldosterone
  - Decreased renin
  - Decreased GFR
  - Increased NaCl and H₂O excretion
- Medulla oblongata
  - Decreased sympathetic output
Potassium Balance

Aldosterone (but not other factors in the RAS pathway) also plays a critical role in potassium homeostasis. Only about 2% of the body’s K⁺ load is in the ECF, but regulatory mechanisms keep plasma K⁺ concentrations within a narrow range (3.5–5 meq/L). Under normal conditions, mass balance matches K⁺ excretion to K⁺ ingestion. If intake exceeds excretion and plasma K⁺ goes up, aldosterone is released into the blood through the direct effect of hyperkalemia on the adrenal cortex. Aldosterone acting on distal-nephron P cells keeps the cells’ apical ion channels open longer and speeds up the Na⁺-K⁺-ATPase pump, enhancing renal excretion of K⁺.

The regulation of body potassium levels is essential to maintaining a state of well-being. Changes in extracellular K⁺ concentration affect the resting membrane potential of all cells. If plasma (and ECF) K⁺ concentrations decrease (hypokalemia), the concentration gradient between the cell and the ECF becomes larger, more K⁺ leaves the cell, and the resting membrane potential becomes more negative. If ECF K⁺ concentrations increase (hyperkalemia), the concentration gradient decreases and more K⁺ remains in the cell, depolarizing it. (Remember that when plasma K⁺ concentrations change, anions such as Cl⁻ are also added to or subtracted from the ECF in a 1:1 ratio, maintaining overall electrical neutrality.)

Because of the effect of plasma K⁺ on excitable tissues, such as the heart, clinicians are always concerned about keeping plasma K⁺ within its normal range. If K⁺ falls below 3 meq/L or rises above 6 meq/L, the excitable tissues of muscle and nerve begin to show altered function. For example, hypokalemia causes muscle weakness because it is more difficult for hyperpolarized neurons and muscles to fire action potentials. The danger in this condition lies in the failure of respiratory muscles and the heart. Fortunately, skeletal muscle weakness is usually significant enough to lead patients to seek treatment before cardiac problems occur. Mild hypokalemia may be corrected by oral intake of K⁺ supplements and K⁺-rich foods, such as orange juice and bananas.

Hyperkalemia is a more dangerous potassium disturbance because in this case depolarization of excitable tissues makes them more excitatory initially. Subsequently, the cells are unable to repolarize fully and actually become less excitable. In this state, they have action potentials that are either smaller than normal or nonexistent. Cardiac muscle excitability affected by changes in plasma K⁺ can lead to life-threatening cardiac arrhythmias.

Disturbances in K⁺ balance may result from kidney disease, eating disorders, loss of K⁺ in diarrhea, or the use of certain types of diuretics that prevent the kidneys from fully reabsorbing K⁺. Inappropriate correction of dehydration can also create K⁺ imbalance. Consider a golfer playing a round of golf when the temperature was above 100 °F. He was aware of the risk of dehydration, so he drank lots of water to replace fluid lost through sweating. The replacement of lost sweat with pure water kept his ECF volume normal but dropped his total blood osmolality and his K⁺ and Na⁺ concentrations. He was unable to finish the round of golf because of muscle weakness, and he required medical attention that included ion replacement therapy. A more suitable replacement fluid would have been one of the sports drinks that include salt and K⁺.

Potassium balance is also closely tied to acid-base balance, as you will learn in the final section of this chapter. Correction of a pH disturbance requires close attention to plasma K⁺ levels. Similarly, correction of K⁺ imbalance may alter body pH.

Behavioral Mechanisms in Salt and Water Balance

Although neural, neuroendocrine, and endocrine reflexes play key roles in salt and water homeostasis, behavioral responses are critical in restoring the normal state, especially when ECF volume decreases or osmolarity increases. Drinking water is normally the only way to restore lost water, and eating salt is the only way to raise the body’s Na⁺ content. Both behaviors are essential for normal salt and water balance. Clinicians must recognize the absence of these behaviors in patients who are unconscious or otherwise unable to obey behavioral urges, and must adjust treatment accordingly. The study of the biological basis for behaviors, including drinking and eating, is a field known as physiological psychology.

Drinking Replaces Fluid Loss

Thirst is one of the most powerful urges known in humans. In 1952, the Swedish physiologist Bengt Andersson showed that stimulating certain regions of the hypothalamus triggered drinking behavior. This discovery led to the identification of hypothalamic osmoreceptors that initiate drinking when body osmolality rises above 280 mOsm/L. This is an example of a behavior initiated by an internal stimulus.

It is interesting to note that although increased osmolarity triggers thirst, the act of drinking is sufficient to relieve thirst. The ingested water need not be absorbed in order for thirst to be quenched. As-yet-unidentified receptors in the mouth and pharynx (oropharynx receptors) respond to cold water by decreasing thirst and decreasing vasopressin release even though plasma osmolality remains high. This oropharynx reflex is one reason surgery patients are allowed to suck on ice chips: the ice alleviates their thirst without putting significant amounts of fluid into the digestive system.
A similar reflex exists in camels. When led to water, they drink just enough to replenish their water deficit. Oropharynx receptors apparently act as a feedforward “metering” system that helps prevent wide swings in osmolarity by matching water intake to water need.

In humans, cultural rituals complicate the thirst reflex. For example, we may drink during social events, whether or not we are thirsty. As a result, our bodies must be capable of eliminating fluid ingested in excess of our physiological needs.

**Concept Check**

13. Incorporate the thirst reflex into Figure 20.8.

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**RUNNING PROBLEM**

During exercise in the heat, sweating rate and sweat composition are quite variable among athletes and depend partly on how acclimatized the individual is to the heat. Sweat fluid losses can range from less than 0.6 L/h to more than 2.5 L/h, and sweat Na⁺ concentrations can range from less than 20 mEq/L to more than 90 mEq/L. The white salt crystals noted on Lauren's face and clothing suggest that she is a "salty sweater" who probably lost a large amount of salt during the race. Follow-up testing revealed that Lauren's sweat Na⁺ concentration was 70 mEq/L.

**Q6:** Assuming a sweating rate of 1 L/hr, how much Na⁺ did Lauren lose during the 16-hour race?

**Q7:** Total body water for a 60-kg female is approximately 30 L, and her ECF volume is 10 L. Based on the information given in the problem so far, calculate how much fluid Lauren probably ingested during the race.

In that respect, maintaining fluid balance is like driving a car down the highway and making small adjustments to keep the car in the center of the lane. However, just as exciting movies feature wild car chases, not sedate driving, the exciting part of fluid homeostasis is the body's response to crisis situations, such as severe dehydration or hemorrhage. In this section we examine challenges to salt and water balance.

**Osmolarity and Volume Can Change Independently**

Normally, volume and osmolarity are homeostatically maintained within an acceptable range. Under some circumstances, however, fluid loss exceeds fluid gain or vice versa, and the body goes out of balance. Common pathways for fluid loss include excessive sweating, vomiting, diarrhea, and hemorrhage. All these situations may require medical intervention. In contrast, fluid gain is seldom a medical emergency, unless it is addition of water that decreases osmolarity below an acceptable range.

Volume and osmolarity of the ECF can each have three possible states: normal, increased, or decreased. The relation of volume and osmolarity changes can be represented by the matrix in Figure 20.12. The center box represents the normal state, and the surrounding boxes represent the most common examples of the variations from normal.

In all cases, the appropriate homeostatic compensation for the change acts according to the principle of mass balance: whatever fluid and solute were added to the body must be removed,
Dehydration is a disturbance (middle row, right cell) might occur if you ate salted popcorn and a soft drink at the movies. The net result could be ingestion of hypertonic saline that increases ECF volume and osmolarity. The appropriate homeostatic response is excretion of isotonic urine. For homeostasis to be maintained, the osmolarity and volume of the urinary output must match the salt and water input from the popcorn and soft drink.

1. Increased volume, increased osmolarity. A state of increased volume and increased osmolarity might occur if you ate salty food and drank liquids at the same time, such as popcorn and a soft drink at the movies. The net result could be ingestion of hypertonic saline that increases ECF volume and osmolarity. The appropriate homeostatic response is excretion of hypertonic urine. For homeostasis to be maintained, the osmolarity and volume of the urinary output must match the salt and water input from the popcorn and soft drink.

2. Increased volume, no change in osmolarity. Moving one cell to the left in the top row, we see that if the proportion of salt and water in ingested food is equivalent to an isotonic NaCl solution, volume increases but osmolarity does not change. The appropriate response is excretion of isotonic urine whose volume equals that of the ingested fluid.

3. Increased volume, decreased osmolarity. This situation would occur if you drank pure water without ingesting any solute. The goal here would be to excrete very dilute urine to maximize water loss while conserving salts. However, because our kidneys cannot excrete pure water, there is always some loss of solute in the urine. In this situation, urinary output cannot exactly match input, and so compensation is imperfect.

4. No change in volume, increased osmolarity. This disturbance (middle row, right cell) might occur if you ate salted popcorn without drinking anything. The ingestion of salt without water increases ECF osmolarity and causes some water to shift from cells to the ECF. The homeostatic response is intense thirst, which prompts ingestion of water to dilute the added solute. The kidneys help by creating highly concentrated urine of minimal volume, conserving water while removing excess NaCl. Once water is ingested, the disturbance becomes that described in situation 1 or situation 2.

5. No change in volume, decreased osmolarity. This scenario (middle row, left cell) might occur when a person who is dehydrated replaces lost fluid with pure water, like the golfer described earlier. The decreased volume resulting from the dehydration is corrected, but the replacement fluid has no solutes to replace those lost. Consequently, a new imbalance is created.

Dehydration has multiple causes. During prolonged heavy exercise, water loss from the lungs can double while sweat loss may increase from 0.1 liter to as much as 5 liters! Because the fluid secreted by sweat glands is hyposmotic, the fluid left behind in the body becomes hyperosmotic.

Diarrhea (diarhein, to flow through), excessively watery feces, is a pathological condition involving major water and solute loss, this time from the digestive tract. In both sweating and diarrhea, if too much fluid is lost from the circulatory system, blood volume decreases to the point that the heart can no longer pump blood effectively to the brain. In addition, cell shrinkage caused by increased osmolarity disrupts cell function.

Dehydration has multiple causes. During prolonged heavy exercise, water loss from the lungs can double while sweat loss may increase from 0.1 liter to as much as 5 liters! Because the fluid secreted by sweat glands is hyposmotic, the fluid left behind in the body becomes hyperosmotic.

Table 20.1

Dehydration Triggers Homeostatic Responses

To understand the body’s integrated response to changes in volume and osmolarity, you must first have a clear idea of which pathways become active in response to various stimuli.
## Responses Triggered by Changes in Volume, Blood Pressure, and Osmolarity

<table>
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<th>Stimulus</th>
<th>Organ or Tissue Involved</th>
<th>Response(s)</th>
<th>Figure(s)</th>
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<td>Renin secretion</td>
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<td><strong>Direct effects</strong></td>
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<td>Glomerulus</td>
<td>Increased GFR (transient)</td>
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<td>Myocardial cells</td>
<td>Natriuretic peptide secretion</td>
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<td><strong>Reflexes</strong></td>
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<td>Carotid and aortic baroreceptors</td>
<td>Cardiovascular control center</td>
<td>Decreased sympathetic output, increased parasympathetic output</td>
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<tr>
<td>Carotid and aortic baroreceptors</td>
<td>Hypothalamus</td>
<td>Thirst inhibition</td>
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<td>Hypothalamus</td>
<td>Vasopressin inhibition</td>
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<td>Vasopressin inhibition</td>
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<td><strong>INCREASED OSMOLARITY</strong></td>
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<td><strong>Direct effects</strong></td>
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<tr>
<td>Pathological dehydration</td>
<td>Adrenal cortex</td>
<td>Decreased aldosterone secretion</td>
<td>20.13</td>
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</table>
several reflex pathways that are mediated through the carotid and aortic baroreceptors and the pressure-sensitive granular cells. Decreased volume is sensed by the atrial volume receptors.

1. The carotid and aortic baroreceptors signal the cardiovascular control center (CVCC) to raise blood pressure. Sympathetic output from the CVCC increases while parasympathetic output decreases.
   (a) Heart rate goes up as control of the SA node shifts from predominantly parasympathetic to sympathetic.
   (b) The force of ventricular contraction also increases under sympathetic stimulation. The increased force of contraction combines with increased heart rate to increase cardiac output.
   (c) Simultaneously, sympathetic input causes arteriolar vasoconstriction, increasing peripheral resistance.
   (d) Sympathetic vasoconstriction of afferent arterioles in the kidneys decreases GFR, helping conserve fluid.
   (e) Increased sympathetic activity at the granular cells of the kidneys increases renin secretion.

Table 20.1 (Continued)

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Organ or Tissue Involved</th>
<th>Response(s)</th>
<th>Figure(s)</th>
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<td>Reflexes</td>
<td>Osmoreceptors</td>
<td>Hypothalamus</td>
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<td>Vasopressin secretion</td>
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<tr>
<td>Direct effects</td>
<td>Pathological hyponatremia</td>
<td>Adrenal cortex</td>
<td>Increased aldosterone secretion</td>
</tr>
</tbody>
</table>

2. Decreased peripheral blood pressure directly decreases GFR. A lower GFR conserves ECF volume by filtering less fluid into the nephron.

3. Paracrine feedback causes the granular cells to release renin. Lower GFR decreases fluid flow past the macula densa. This triggers renin release.

4. Granular cells respond to decreased blood pressure by releasing renin. The combination of decreased blood pressure, increased sympathetic input onto granular cells, and

is a summary of the many pathways involved in the homeostasis of salt and water balance. For details of individual pathways, refer to the figures cited in Table 20.1.

The homeostatic response to severe dehydration is an excellent example of how the body works to maintain blood volume and cell volume in the face of decreased volume and increased osmolarity. It also illustrates the role of neural and endocrine integrating centers. In severe dehydration, the adrenal cortex receives two opposing signals. One says, “Secret aldosterone”; the other says, “Do not secrete aldosterone.” The body has multiple mechanisms for dealing with diminished blood volume, but high ECF osmolality causes cells to shrink and presents a more immediate threat to well-being. Thus, faced with decreased volume and increased osmolarity, the adrenal cortex does not secrete aldosterone. (If secreted, aldosterone would cause Na$^+$ reabsorption, which could worsen the already-high osmolarity associated with dehydration.)

In severe dehydration, compensatory mechanisms are aimed at restoring normal blood pressure, ECF volume, and osmolarity by (1) conserving fluid to prevent additional loss, (2) triggering cardiovascular reflexes to increase blood pressure, and (3) stimulating thirst so that normal fluid volume and osmolarity can be restored. Figure 20.13 maps the interwoven nature of these responses. This figure is complex and intimidating at first glance, so let’s discuss it step by step.

At the top of the map (in yellow) are the two stimuli caused by dehydration: decreased blood volume/pressure, and increased osmolarity. Decreased ECF volume causes decreased blood pressure. Blood pressure acts both directly and as a stimulus for several reflex pathways that are mediated through the carotid and aortic baroreceptors and the pressure-sensitive granular cells. Decreased volume is sensed by the atrial volume receptors.
HOMEOSTATIC COMPENSATION FOR SEVERE DEHYDRATION

DEHYDRATION

Blood volume/
Blood pressure

accompanied by

Osmolarity

CARDOVASCULAR
MECHANISMS

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Cardiac output

Blood pressure

Volume

Osmolarity

Renin-angiotensin system

Renal mechanisms

Hypothalamic mechanisms

Hypothalamic osmoreceptors

vasopressin

Angiotensinogen

ACE

Angiotensin II

Aldosterone

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Parasympathetic output

Sympathetic output

Heart

Arterioles

Atrial volume receptors; Carotid and aortic baroreceptors

Hypothalamus

Vasopressin release from posterior pituitary

ANG I

Renin

Angiotensinogen

ACE

ANG II

Adrenal cortex

Aldosterone

Distal nephron

Na+ reabsorption

Distal nephron

H2O reabsorption

H2O intake

Osmolarity

Fig. 20.13
signals from the macula densa stimulates renin release and ensures increased production of ANG II.

5. **Decreased blood pressure, decreased blood volume, increased osmolarity, and increased ANG II production all stimulate vasopressin and the thirst centers of the hypothalamus.**

The redundancy in the control pathways ensures that all four main compensatory mechanisms are activated: cardiovascular responses, ANG II, vasopressin, and thirst.

1. **Cardiovascular responses** combine increased cardiac output and increased peripheral resistance to raise blood pressure. Note, however, that this increase in blood pressure does *not necessarily* mean that blood pressure returns to normal. If dehydration is severe, compensation may be incomplete, and blood pressure may remain below normal.

2. **Angiotensin II** has a variety of effects aimed at raising blood pressure, including stimulation of thirst, vasopressin release, direct vasoconstriction, and reinforcement of cardiovascular control center output. ANG II also reaches the adrenal cortex and attempts to stimulate aldosterone release. In dehydration, however, Na⁺ reabsorption worsens the already high osmolarity. Consequently, high osmolarity at the adrenal cortex directly inhibits aldosterone release, blocking the action of ANG II. The RAS pathway in dehydration produces the beneficial blood pressure-enhancing effects of ANG II while avoiding the detrimental effects of Na⁺ reabsorption. This is a beautiful example of integrated function.

3. **Vasopressin** increases the water permeability of the renal collecting ducts, allowing water reabsorption to conserve fluid. Without fluid replacement, however, vasopressin cannot bring volume and osmolarity back to normal.

4. **Oral (or intravenous) intake of water** in response to thirst is the only mechanism for replacing lost fluid volume and for restoring ECF osmolarity to normal.

The net result of all four mechanisms is (1) restoration of volume by water conservation and fluid intake, (2) maintenance of blood pressure through increased blood volume, increased cardiac output, and vasoconstriction, and (3) restoration of normal osmolarity by decreased Na⁺ reabsorption and increased water reabsorption and intake.

Using the pathways listed in Table 20.1 and Figure 20.13 as a model, try to create reflex maps for the seven other disturbances of volume and osmolarity shown in Figure 20.12.

**Acid-Base Balance**

Acid-base balance (also called pH homeostasis) is one of the essential functions of the body. The pH of a solution is a measure of its H⁺ concentration. The H⁺ concentration of normal arterial plasma sample is 0.00004 meq/L, minute compared with the concentrations of other ions. (For example, the plasma concentration of Na⁺ is about 135 meq/L.)

Because the body's H⁺ concentration is so low, it is commonly expressed on a logarithmic pH scale of 0–14, in which a pH of 7.0 is neutral (neither acidic nor basic). If the pH of a solution is below 7.0, the solution has an H⁺ concentration greater than $1 \times 10^{-7}$ M and is considered acidic. If the pH is above 7.0, the solution has an H⁺ concentration lower than $1 \times 10^{-7}$ M and is considered alkaline (basic).

The normal pH of the body is 7.40, slightly alkaline. A change of 1 pH unit represents a 10-fold change in H⁺ concentration.

**pH Changes Can Denature Proteins**

The normal pH range of plasma is 7.38–7.42. Extracellular pH usually reflects intracellular pH, and vice versa. Because monitoring intracellular conditions is difficult, plasma values are used clinically as an indicator of ECF and whole body pH. Body fluids that are “outside” the body’s internal environment, such as those in the lumen of the gastrointestinal tract or kidney tubule, can have a pH that far exceeds the normal range. Acidic secretions in the stomach, for instance, may create a gastric pH as low as 1, and the pH of urine varies between 4.5 and 8.5, depending on the body’s need to excrete H⁺ or HCO₃⁻.

The concentration of H⁺ in the body is closely regulated. Intracellular proteins, such as enzymes and membrane channels, are particularly sensitive to pH because the function of these proteins depends on their three-dimensional shape. Changes in H⁺ concentration alter the tertiary structure of proteins by interacting with hydrogen bonds in the molecules, disrupting the proteins’ three-dimensional structures and activities. Abnormal pH may significantly affect the activity of the nervous system. If pH is too low—the condition known as **acidosis**—neurons become less excitable, and CNS depression results. Patients become confused and disoriented, then slip into a coma. If CNS depression progresses, the respiratory centers cease to function, causing death.

If pH is too high—the condition known as **alkalosis**—neurons become hyperexcitable, firing action potentials at the slightest signal. This condition shows up first as sensory changes, such as numbness or tingling, then as muscle twitches. If alkalosis is severe, muscle twitches turn into sustained contractions (tetanus) that paralyze respiratory muscles.

Disturbances of acid-base balance are associated with disturbances in K⁺ balance. This is partly due to a renal transporter that moves K⁺ and H⁺ ions in an antiport fashion. In acidosis, the kidneys excrete H⁺ and reabsorb K⁺ using an H⁺-K⁺-ATPase. In alkalosis, the kidneys reabsorb H⁺ and excrete K⁺. Potassium imbalance usually shows up as disturbances in excitable tissues, especially the heart.
Acids and Bases in the Body Come from Many Sources

In day-to-day functioning, the body is challenged by intake and production of acids more than bases. Hydrogen ions come both from food and from internal metabolism. Maintaining mass balance requires that acid intake and production be balanced by acid excretion. Hydrogen balance in the body is summarized in Figure 20.14.

**Acid Input** Many metabolic intermediates and foods are organic acids that ionize and contribute $H^+$ to body fluids.* Examples of organic acids include amino acids, fatty acids, intermediates in the citric acid cycle, and lactate produced by anaerobic metabolism. Metabolic production of organic acids each day generates a significant amount of $H^+$ that must be excreted to maintain mass balance.

Under extraordinary circumstances, metabolic organic acid production can increase significantly and create a crisis. For example, severe anaerobic conditions, such as circulatory collapse, produce so much lactate that normal homeostatic mechanisms cannot keep pace, resulting in a state of *lactic acidosis.* In diabetes mellitus, abnormal metabolism of fats and amino acids creates strong acids known as *ketoacids.* These acids cause a state of metabolic acidosis known as *ketoacidosis.*

The biggest source of acid on a daily basis is the production of $CO_2$ during aerobic respiration. Carbon dioxide is not an acid because it does not contain any hydrogen atoms. However, $CO_2$ from respiration combines with water to form carbonic acid ($H_2CO_3$), which dissociates into $H^+$ and bicarbonate ion, $HCO_3^-$.

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

This reaction takes place in all cells and in the plasma, but at a slow rate. However, in certain cells of the body, the reaction proceeds very rapidly because of the presence of large amounts of carboxic anhydrase. This enzyme catalyzes the conversion of $CO_2$ and $H_2O$ to $H^+$ and $HCO_3^-$.

The production of $H^+$ from $CO_2$ and $H_2O$ is the single biggest source of acid input under normal conditions. By some estimates, $CO_2$ from resting metabolism produces $12,500$ meq of $H^+$ each day. If this amount of acid were placed in a volume of water equal to the plasma volume, it would create an $H^+$ concentration of $4167$ meq/L, over one hundred million ($10^8$) times as concentrated as the normal plasma $H^+$ concentration of $0.00004$ meq/L!

These numbers show that $CO_2$ from aerobic respiration has the potential to affect pH in the body dramatically. Fortunately, homeostatic mechanisms normally prevent $CO_2$ from accumulating in the body.

**Base Input** Acid-base physiology focuses on acids for good reasons. First, our diet and metabolism have few significant sources of bases. Some fruits and vegetables contain anions that metabolize to $HCO_3^-$, but the influence of these foods is far outweighed by the contribution of acidic fruits, amino acids, and fatty acids. Second, acid-base disturbances due to excess acid are more common than those due to excess base. For these reasons, the body expends far more resources removing excess acid.

**pH Homeostasis Depends on Buffers, Lungs, and Kidneys**

How does the body cope with minute-to-minute changes in pH? There are three mechanisms: (1) buffers, (2) ventilation, and (3) renal regulation of $H^+$ and $HCO_3^-$. Buffers are the first line of defense, always present and waiting to prevent wide swings in pH. Ventilation, the second line of defense, is a rapid, reflexively controlled response that can take care of 75% of most pH disturbances. The final line of defense lies with the kidneys. They are slower than buffers or the lungs but are very effective at coping with any remaining pH disturbance under normal conditions. Usually these three mechanisms help the body balance acid so effectively that normal body pH varies only slightly. Let’s take a closer look at each of them.

---

*The anion forms of many organic acids end with the suffix –ate, such as pyruvate and lactate.*
Buffer Systems Include Proteins, Phosphate Ions, and HCO$_3^-$

A buffer is a molecule that moderates but does not prevent changes in pH by combining with or releasing H$^+$. In the absence of buffers, the addition of acid to a solution causes a sharp change in pH. In the presence of a buffer, the pH change is moderated or may even be unnoticeable. Because acid production is the major challenge to pH homeostasis, most physiological buffers combine with H$^+$.

Buffers are found both within cells and in the plasma. Intracellular buffers include cellular proteins, phosphate ions (HPO$_4^{2-}$), and hemoglobin. Hemoglobin in red blood cells buffers the H$^+$ produced by the reaction of CO$_2$ with H$_2$O.

Each H$^+$ ion buffered by hemoglobin leaves a matching bicarbonate ion inside the red blood cell. This HCO$_3^-$ can then leave the red blood cell in exchange for plasma Cl$^-$, the chloride shift.

The large amounts of plasma bicarbonate produced from metabolic CO$_2$ create the most important extracellular buffer system of the body. Plasma HCO$_3^-$ concentration averages 24 meq/L, which is approximately 600,000 times as concentrated as plasma H$^+$. Although H$^+$ and HCO$_3^-$ are created in a 1:1 ratio from CO$_2$ and H$_2$O, intracellular buffering of H$^+$ by hemoglobin is a major reason the two ions do not appear in the plasma in the same concentration. The HCO$_3^-$ in plasma is then available to buffer H$^+$ from nonrespiratory sources, such as metabolism.

The relationship between CO$_2$, HCO$_3^-$, and H$^+$ in the plasma is expressed by the equation we just looked at:

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- \quad (1)
\]

According to the law of mass action, any change in the amount of CO$_2$, H$^+$, or HCO$_3^-$ in the reaction solution causes the reaction to shift until a new equilibrium is reached. (Water is always in excess in the body and does not contribute to the reaction equilibrium.) For example, if CO$_2$ increases (red), the equation shifts to the right, creating one additional H$^+$ and one additional HCO$_3^-$ from each CO$_2$ and water:

\[
\uparrow\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \uparrow\text{H}^+ + \uparrow\text{HCO}_3^- \quad (2)
\]

Once a new equilibrium is reached, both H$^+$ and HCO$_3^-$ levels have increased. The addition of H$^+$ makes the solution more acidic and therefore lowers its pH. In this reaction, it does not matter that a HCO$_3^-$ buffer molecule has also been produced because HCO$_3^-$ acts as a buffer only when it binds to H$^+$ and becomes carbonic acid.

Now suppose H$^+$ (red) is added to the plasma from some metabolic source, such as lactic acid:

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \uparrow\text{H}^+ + \text{HCO}_3^- \quad (3)
\]

In this case, plasma HCO$_3^-$ can act as a buffer by combining with some of the added H$^+$ until the reaction reaches a new equilibrium state. The increase in H$^+$ shifts the equation to the left:

\[
\text{CO}_2 + \text{H}_2\text{O} \leftarrow \text{H}_2\text{CO}_3 \leftarrow \uparrow\text{H}^+ + \downarrow\text{HCO}_3^- \quad (4)
\]

Converting some of the added H$^+$ and bicarbonate buffer to carbonic acid means that at equilibrium, H$^+$ is still elevated, but not as much as it was initially. The concentration of HCO$_3^-$ is decreased because some has been used as a buffer. The buffered H$^+$ is converted to CO$_2$ and H$_2$O$_2$, increasing the amounts of both. At equilibrium, the reaction looks like this:

\[
\uparrow\text{CO}_2 + \uparrow\text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \uparrow\text{H}^+ + \downarrow\text{HCO}_3^- \quad (5)
\]

The law of mass action is a useful way to think about the relationship between changes in the concentrations of H$^+$, HCO$_3^-$, and CO$_2$, as long as you remember certain qualifications. First, a change in HCO$_3^-$ concentration (as indicated in reaction 5) may not show up clinically as a HCO$_3^-$ concentration outside the normal range. This is because HCO$_3^-$ is 600,000 times more concentrated in the plasma than H$^+$. If both H$^+$ and HCO$_3^-$ are added to the plasma, you may observe changes in pH but not in HCO$_3^-$ concentration because so much bicarbonate was present initially. Both H$^+$ and HCO$_3^-$ experience an absolute increase in concentration, but because so many HCO$_3^-$ were in the plasma to begin with, the relative increase in HCO$_3^-$ goes unnoticed.

As an analogy, think of two football teams playing in a stadium packed with 80,000 fans. If 10 more players (H$^+$) run out onto the field, everyone notices. But if 10 people (HCO$_3^-$) come into the stands at the same time, no one pays any attention because there were already so many people watching the game that 10 more make no significant difference.

The relationship between pH, HCO$_3^-$ concentration in mM, and dissolved CO$_2$ concentration is expressed mathematically...
by the Henderson-Hasselbalch equation. One variant of the equation that is more useful in clinical medicine uses $P_{CO_2}$ instead of dissolved $CO_2$ concentration:

$$ \text{pH} = 6.1 + \log\left[\frac{HCO_3^-}{P_{CO_2}/0.03}\right] $$

If you know a patient’s $P_{CO_2}$ and plasma bicarbonate concentration, you can predict the plasma pH.

The second qualification for the law of mass action is that when the reaction shifts to the left and increases plasma $CO_2$, a nearly instantaneous increase in ventilation takes place in a normal person. If extra $CO_2$ is ventilated off, arterial $P_{CO_2}$ may remain normal or even fall below normal as a result of hyperventilation.

**Ventilation Can Compensate for pH Disturbances**

The increase in ventilation just described is a respiratory compensation for acidosis. Ventilation and acid-base status are intimately linked, as shown by the equation:

$$ CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- $$

Changes in ventilation can correct disturbances in acid-base balance, but they can also cause them. Because of the dynamic equilibrium between $CO_2$ and $H^+$, any change in plasma $P_{CO_2}$ affects both $H^+$ and $HCO_3^-$ content of the blood.

For example, if a person hypoventilates and $P_{CO_2}$ increases (red), the equation shifts to the right. More carbonic acid is formed, and $H^+$ goes up, creating a more acidotic state:

$$ \uparrow CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow \uparrow H^+ + \uparrow HCO_3^- $$

On the other hand, if a person hyperventilates, blowing off $CO_2$ and thereby decreasing the plasma $P_{CO_2}$ (red), the equation shifts to the left, which means that $H^+$ combines with $HCO_3^-$ and becomes carbonic acid, thereby decreasing the $H^+$ concentration. Lower $H^+$ means an increase in pH:

$$ \downarrow CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow \downarrow H^+ + \downarrow HCO_3^- $$

In these two examples, you can see that a change in $P_{CO_2}$ affects the $H^+$ concentration and therefore the pH of the plasma. The body uses ventilation as a method for adjusting pH only if a stimulus associated with pH triggers the reflex response. Two stimuli can do so: $H^+$ and $CO_2$.

Ventilation is affected directly by plasma $H^+$ levels through carotid and aortic chemoreceptors (Fig. 20.15). These chemoreceptors are located in the aorta and carotid arteries along with oxygen sensors and blood pressure sensors. An increase in plasma $H^+$ stimulates the chemoreceptors, which in turn signal the medullary respiratory control centers to increase ventilation. Increased alveolar ventilation allows the lungs to excrete more $CO_2$ and convert $H^+$ to carbonic acid.

The central chemoreceptors of the medulla oblongata cannot respond directly to changes in plasma pH because $H^+$ does not cross the blood-brain barrier. However, changes in pH change $P_{CO_2}$, and $CO_2$ stimulates the central chemoreceptors. Dual control of ventilation through the central and peripheral chemoreceptors helps the body respond rapidly to changes in either pH or plasma $CO_2$.

**Kidneys Use Ammonia and Phosphate Buffers**

The kidneys take care of the 25% of compensation that the lungs cannot handle. They alter pH two ways: (1) directly, by excreting or reabsorbing $H^+$ and (2) indirectly, by changing the rate at which $HCO_3^-$ buffer is reabsorbed or excreted.

In acidosis, the kidney secretes $H^+$ into the tubule lumen using direct and indirect active transport (Fig. 20.16). Ammonia from amino acids and phosphate ions ($HPO_4^{2-}$) in the kidney act as buffers, trapping large amounts of $H^+$ as $NH_4^+$ and $H_2PO_4^-$. These buffers allow more $H^+$ to be excreted. Phosphate ions are present in filtrate and combine with $H^+$ secreted into the nephron lumen:

$$ HPO_4^{2-} + H^+ \rightleftharpoons H_2PO_4^- $$

Even with these buffers, urine can become quite acidic, down to a pH of about 4.5. While $H^+$ is being excreted, the kidneys make new $HCO_3^-$ from $CO_2$ and $H_2O$. The $HCO_3^-$ is reabsorbed into the blood to act as a buffer and increase pH.

In alkalosis, the kidney reverses the general process just described for acidosis, excreting $HCO_3^-$ and reabsorbing $H^+$ in an effort to bring pH back into the normal range. Renal compensations are slower than respiratory compensations, and their effect on pH may not be noticed for 24–48 hours. However, once activated, renal compensations effectively handle all but severe acid-base disturbances.

The cellular mechanisms for renal handling of $H^+$ and $HCO_3^-$ resemble transport processes in other epithelia. However, these mechanisms involve some membrane transporters that you have not encountered before:

1. The apical $Na^+-H^+$ exchanger (NHE) is an indirect active transporter that brings $Na^+$ into the epithelial cell in exchange for moving $H^+$ against its concentration gradient into the lumen. This transporter also plays a role in proximal tubule $Na^+$ reabsorption.
The Proximal Tubule Secretes $\text{H}^+$ and Reabsorbs $\text{HCO}_3^-$

The amount of bicarbonate ion the kidneys filter each day is equivalent to the bicarbonate in a pound of baking soda (NaHCO$_3$)! Most of this HCO$_3^-$ must be reabsorbed to maintain the body’s buffer capacity. The proximal tubule reabsorbs most filtered HCO$_3^-$ by indirect methods because there is no apical membrane transporter to bring HCO$_3^-$ into the tubule cell.

Figure 20.17a shows the two pathways by which bicarbonate is reabsorbed in the proximal tubule. (The numbers in the following lists correspond to the steps shown in the figure.) By following this illustration, you will see how the transporters listed in the previous section function together.

1. $\text{H}^+$ is secreted from the proximal tubule cell into the lumen in exchange for filtered Na$^+$, which moves from the...
The kidney secretes H+, which is buffered in the urine by ammonia and phosphate ions. It reabsorbs bicarbonate to act as an extracellular buffer.

**The Distal Nephron Controls Acid Excretion**

The distal nephron plays a significant role in the fine regulation of acid-base balance. The intercalated cells (or I cells) interspersed among the principal cells are responsible for acid-base regulation.

Intercalated cells are characterized by high concentrations of carbonic anhydrase in their cytoplasm. This enzyme allows them to rapidly convert CO₂ and water into H⁺ and HCO₃⁻. The H⁺ ions are pumped out of the intercalated cell either by the H⁺-ATPase or by an ATPase that exchanges one H⁺ for one K⁺. Bicarbonate leaves the cell by means of the HCO₃⁻-Cl⁻ antiport exchanger.

There are two types of intercalated cells, and their transporters are found on different faces of the epithelial cell. During periods of acidosis, type A intercalated cells secrete H⁺ and reabsorb bicarbonate. During periods of alkalosis, type B intercalated cells secrete HCO₃⁻ and reabsorb H⁺.

Figure 20.17b shows how type A intercalated cells work during acidosis, secreting H⁺ and reabsorbing HCO₃⁻. The process is similar to H⁺ secretion in the proximal tubule except for the specific H⁺ transporters. The distal nephron uses apical H⁺-ATPase and H⁺-K⁺-ATPase rather than the Na⁺-H⁺ antiport protein found in the proximal tubule.

During alkalosis, when the H⁺ concentration of the body is too low, H⁺ is reabsorbed and HCO₃⁻ buffer is excreted in the urine (Fig. 20.17c). Once again, the ions are formed from H₂O and CO₂. Hydrogen ions are reabsorbed by transport into the ECF on the basolateral side of the cell, and HCO₃⁻ is secreted into the lumen. The polarity of the two types of I cells is reversed, with the same transport processes taking place, but on the opposite sides of the cell.

The H⁺-K⁺-ATPase of the distal nephron helps create parallel disturbances of acid-base balance and K⁺ balance. In acidosis, when plasma H⁺ is high, the kidney secretes H⁺ and reabsorbs K⁺. For this reason, acidosis is often accompanied by hyperkalemia. (Other nonrenal events also contribute to elevated ECF K⁺ concentrations in acidosis.) The reverse is true for alkalosis, when blood H⁺ levels are low. The mechanism that allows the distal nephron to reabsorb H⁺ simultaneously causes it to secrete K⁺, with the result that alkalosis goes hand in hand with hypokalemia.
(a) Proximal tubule reabsorption of filtered $\text{HCO}_3^-$.

1. NHE secretes $\text{H}^+$.
2. $\text{H}^+$ in filtrate combines with filtered $\text{HCO}_3^-$ to form $\text{CO}_2$.
3. $\text{CO}_2$ diffuses into cell.
4. $\text{CO}_2$ combines with water to form $\text{H}^+$ and $\text{HCO}_3^-$.
5. $\text{H}^+$ is secreted again.
6. $\text{HCO}_3^-$ is reabsorbed with $\text{Na}^+$.
7. Glutamine is metabolized to ammonium ion and $\text{HCO}_3^-$.
8. NH$_4^+$ is secreted and excreted.

(b) Acidosis. Type A intercalated cells in collecting duct function in acidosis. $\text{H}^+$ is excreted; $\text{HCO}_3^-$ and $\text{K}^+$ are reabsorbed.

(c) Alkalosis. Type B intercalated cells in collecting duct function in alkalosis. $\text{HCO}_3^-$ and $\text{K}^+$ are excreted; $\text{H}^+$ is reabsorbed.
Acid-Base Disturbances May Be Respiratory or Metabolic

The three compensatory mechanisms (buffers, ventilation, and renal excretion) take care of most variations in plasma pH. But under some circumstances, the production or loss of H⁺ or HCO₃⁻ is so extreme that compensatory mechanisms fail to maintain pH homeostasis. In these states, the pH of the blood moves out of the normal range of 7.38–7.42. If the body fails to keep pH between 7.00 and 7.70, acidosis or alkalosis can be fatal (Fig. 20.18).

Acid-base problems are classified both by the direction of the pH change (acidosis or alkalosis) and by the underlying cause (metabolic or respiratory). Changes in P_CO₂, resulting from hyperventilation or hypoventilation, cause pH to shift. These disturbances are said to be of respiratory origin. If the pH problem arises from acids or bases of non-CO₂ origin, the problem is said to be a metabolic problem.

Note that by the time an acid-base disturbance becomes evident as a change in plasma pH, the body’s buffers are inefficient. The loss of buffering ability leaves the body with only two options: respiratory compensation or renal compensation. And if the problem is of respiratory origin, only one homeostatic compensation is available—the kidneys. If the problem is of metabolic origin, both respiratory and renal mechanisms can compensate. Compensation can bring the pH back closer to normal but may not correct the disturbance completely (Fig. 20.18).

The combination of an initial pH disturbance and the resultant compensatory changes is one factor that makes analysis of acid-base disorders in the clinical setting so difficult. In this course we concentrate on simple scenarios with a single underlying cause. Changes that occur in the four simple acid-base disturbances are listed in Table 20.2.

**Table 20.2**

<table>
<thead>
<tr>
<th>Disturbance</th>
<th>P_CO₂</th>
<th>H⁺</th>
<th>pH</th>
<th>HCO₃⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acidosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Normal* or ↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Alkalosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Normal* or ↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

*These values are different from what you would expect from the law of mass action because almost instantaneous respiratory compensation keeps P_CO₂ from changing significantly.
**Respiratory Acidosis**  A state of respiratory acidosis occurs when alveolar hypventilation results in CO\textsubscript{2} retention and elevated plasma P\textsubscript{CO\textsubscript{2}}. Some situations in which this occurs are respiratory depression due to drugs (including alcohol), increased airway resistance in asthma, impaired gas exchange in fibrosis or severe pneumonia, and muscle weakness in muscular dystrophy and other muscle diseases. The most common cause of respiratory acidosis is chronic obstructive pulmonary disease (COPD), which includes emphysema. In emphysema inadequate alveolar ventilation is compounded by loss of alveolar exchange area.

No matter what the cause of respiratory acidosis, plasma CO\textsubscript{2} levels increase (red), leading to elevated H\textsuperscript{+} and HCO\textsubscript{3}\textsuperscript{-}:

\[
\ce{\text{HCO}_3^- + H_2O & -> H_2CO_3 & -> H^+ + HCO_3^-}
\]

The hallmark of respiratory acidosis is decreased pH with elevated bicarbonate levels (Tbl. 20.2). Because the problem is of respiratory origin, the body cannot carry out respiratory compensation. (However, depending on the problem, mechanical ventilation can sometimes be used to assist breathing.)

Any compensation for respiratory acidosis must occur through renal mechanisms that excrete H\textsuperscript{+} and reabsorb HCO\textsubscript{3}\textsuperscript{-}. The excretion of H\textsuperscript{+} raises plasma pH. Reabsorption of HCO\textsubscript{3}\textsuperscript{-} provides additional buffer that combines with H\textsuperscript{+}, lowering the H\textsuperscript{+} concentration and therefore raising the pH.

In chronic obstructive pulmonary disease, renal compensation mechanisms for acidosis can moderate the pH change, but they may not be able to return the pH to its normal range. If you look at pH and HCO\textsubscript{3}\textsuperscript{-} levels in patients with compensated respiratory acidosis, you find that both those values are closer to normal than they were when the acidosis was at its worst.

**Metabolic Acidosis**  Metabolic acidosis is a disturbance of mass balance that occurs when the dietary and metabolic input of H\textsuperscript{+} exceeds H\textsuperscript{+} excretion. Metabolic causes of acidosis include lactic acidosis, which is a result of anaerobic metabolism, and ketoacidosis, which results from excessive breakdown of fats or certain amino acids. The metabolic pathway that produces ketooic acids is associated with type 1 diabetes mellitus and with low-carbohydrate diets, like the Atkins diet. Ingested substances that cause metabolic acidosis include methanol, aspirin, and ethylene glycol (antifreeze).

Metabolic acidosis is expressed by the equation

\[
\ce{\text{HCO}_3^- + H_2O & -> H_2CO_3 & <-> H^+ + HCO_3^-}
\]

Hydrogen ion concentration increases (red) because of the H\textsuperscript{+} contributed by the metabolic acids. This increase shifts the equilibrium represented in the equation to the left, increasing CO\textsubscript{2} levels and using up HCO\textsubscript{3}\textsuperscript{-} buffer.

Metabolic acidosis can also occur if the body loses HCO\textsubscript{3}\textsuperscript{-}. The most common cause of bicarbonate loss is diarrhea, during which HCO\textsubscript{3}\textsuperscript{-} is lost from the intestines. The pancreas produces HCO\textsubscript{3}\textsuperscript{-} from CO\textsubscript{2} and H\textsubscript{2}O by a mechanism similar to the renal mechanism illustrated in Figure 20.16. The H\textsuperscript{+} made at the same time is released into the blood. Normally, the HCO\textsubscript{3}\textsuperscript{-} is released into the small intestine, then reabsorbed into the blood, buffering the H\textsuperscript{+}. However, if a person is experiencing diarrhea, HCO\textsubscript{3}\textsuperscript{-} is not reabsorbed, and a state of acidosis may result.

Whether HCO\textsubscript{3}\textsuperscript{-} concentration is elevated or decreased is an important criterion for distinguishing metabolic acidosis from respiratory acidosis (Tbl. 20.2).

You would think from looking at equation 9 that metabolic acidosis would be accompanied by elevated P\textsubscript{CO\textsubscript{2}}. However, unless the individual also has a lung disease, respiratory compensation takes place almost instantaneously. Both elevated CO\textsubscript{2} and elevated H\textsuperscript{+} stimulate ventilation through the pathways described earlier. As a result, P\textsubscript{CO\textsubscript{2}} decreases to normal or even below-normal levels due to hyperventilation.

Uncompensated metabolic acidosis is rarely seen clinically. Actually, a common sign of metabolic acidosis is hyperventilation, evidence of respiratory compensation occurring in response to the acidosis.

The renal compensations discussed for respiratory acidosis also take place in metabolic acidosis: secretion of H\textsuperscript{+} and reabsorption of HCO\textsubscript{3}\textsuperscript{-}. Renal compensations take several days to reach full effectiveness, and so they are not usually seen in recent-onset (acute) disturbances.

**Respiratory Alkalosis**  States of alkalosis are much less common than acidic conditions. Respiratory alkalosis occurs as a result of hyperventilation, when alveolar ventilation increases without a matching increase in metabolic CO\textsubscript{2} production. Consequently, plasma P\textsubscript{CO\textsubscript{2}} falls (red), and alkalosis results when the equation shifts to the left:

\[
\ce{\text{HCO}_3^- + H_2O & <-> H_2CO_3 & <-> H^+ + HCO_3^-}
\]

The decrease in CO\textsubscript{2} shifts the equilibrium to the left, and both plasma H\textsuperscript{+} and plasma HCO\textsubscript{3}\textsuperscript{-} decrease. Low plasma HCO\textsubscript{3}\textsuperscript{-} levels in alkalosis indicate a respiratory disorder.

The primary clinical cause of respiratory alkalosis is excessive artificial ventilation. Fortunately, this condition is easily corrected by adjusting the ventilator. The most common physiological cause of respiratory alkalosis is hysterical hyperventilation caused by anxiety. When this is the case, the neurological symptoms caused by alkalosis can be partially reversed by having the patient breathe into a paper bag. In doing so, the patient rebreathes exhaled CO\textsubscript{2}, a process that raises arterial P\textsubscript{CO\textsubscript{2}}, and corrects the problem.

Because this alkalosis has respiratory cause, the only compensation available to the body is renal. Filtered bicarbonate, which if reabsorbed could act as a buffer and increase pH even more, is not reabsorbed in the proximal tubule and is secreted in the distal nephron. The combination of HCO\textsubscript{3}\textsuperscript{-} excretion and H\textsuperscript{+} reabsorption in the distal nephron decreases the body’s HCO\textsubscript{3}\textsuperscript{-} and increases its H\textsuperscript{+}, both of which help correct the alkalosis.
**Metabolic Alkalosis** Metabolic alkalosis has two common causes: excessive vomiting of acidic stomach contents and excessive ingestion of bicarbonate-containing antacids. In both cases, the resulting alkalosis reduces H⁺ concentration (red):

\[
\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^- \quad (11)
\]

The decrease in H⁺ shifts the equilibrium to the right, meaning that carbon dioxide (P\text{CO}_2) decreases and HCO₃⁻ goes up.

Just as in metabolic acidosis, respiratory compensation for metabolic alkalosis is rapid. The increase in pH and drop in P\text{CO}_2 depress ventilation. Hypoventilation means the body retains CO₂, raising the P\text{CO}_2 and creating more H⁺ and HCO₃⁻. This respiratory compensation helps correct the pH problem but elevates HCO₃⁻ levels even more. However, this respiratory compensation is limited because hypoventilation also causes hypoxia. Once the arterial P\text{O}_2 drops below 60 mm Hg, hypoventilation ceases.

The renal response to metabolic alkalosis is the same as that for respiratory alkalosis: HCO₃⁻ is excreted and H⁺ is reabsorbed.

This chapter has used fluid balance and acid-base balance to illustrate functional integration in the cardiovascular, respiratory, and renal systems. Changes in body fluid volume, reflected by changes in blood pressure, trigger both cardiovascular and renal homeostatic responses. Disturbances of acid-base balance are met with compensatory responses from both the respiratory and renal systems. Because of the interwoven responsibilities of these three systems, a disturbance in one system is likely to cause disturbances in the other two. Recognition of this fact is an important aspect of treatment for many clinical conditions.

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**RUNNING PROBLEM CONCLUSION**

**Hyponatremia**

In acute cases of dilutional hyponatremia such as Lauren’s, the treatment goal is to correct the body’s depleted Na⁺ load and raise the plasma osmolarity to reduce cerebral swelling. The physicians in the emergency medical tent started a slow intravenous drip of 3% saline and restricted Lauren’s oral fluid intake. Over the course of several hours, the combination of Na⁺ intake and excretion of dilute urine returned Lauren’s plasma Na⁺ to normal levels.

Hyponatremia has numerous causes, including inappropriate secretion of antidiuretic hormone (a condition known as SIADH, which stands for Syndrome of Inappropriate antidiuretic hormone secretion). To learn more about medical causes of hyponatremia, Google hyponatremia. To learn more about exercise-associated hyponatremia, visit the Gatorade Sports Science Institute at www.gssiweb.com.

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<table>
<thead>
<tr>
<th>Question</th>
<th>Facts</th>
<th>Integration and Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Name the two major body fluid compartments and give the major ions in each compartment.</td>
<td>The major compartments are the intracellular fluid (ICF) and extracellular fluid (ECF) compartments. The primary ICF ion is K⁺, and the major ECF ions are Na⁺ and Cl⁻.</td>
<td>N/A*</td>
</tr>
<tr>
<td>2. Based on Lauren’s history, give a reason for why her weight increased during the race.</td>
<td>Lauren reported drinking lots of water and sports drinks. One liter of pure water has a mass of 1 kg.</td>
<td>Lauren’s fluid intake was greater than her fluid loss from sweating. A 2-kg increase in body weight means she drank an excess of about 2 L.</td>
</tr>
<tr>
<td>3. Which body fluid compartment is being diluted in dilutional hyponatremia?</td>
<td>Ingested water distributes itself throughout the ECF and ICF. Sodium is one of the major extracellular cations.</td>
<td>Lauren consumed a large amount of Na⁺-free fluid and therefore diluted her Na⁺ stores. However, the body compartments are in osmotic equilibrium so both ECF and ICF have lower osmolarities.</td>
</tr>
<tr>
<td>4. One way to estimate osmolarity is to double the plasma Na⁺ concentration. Estimate Lauren’s osmolarity and explain what effect the dilutional hyponatremia has on her cells.</td>
<td>Lauren’s plasma Na⁺ is 124 mEq/L. For Na⁺, 1 mEq = 1 millimole. Doubling this value tells you that Lauren’s estimated plasma osmolarity is 248 mOsm. Water distributes to maintain osmotic equilibrium.</td>
<td>At the start of the race, Lauren’s cells were at 280 mOsm. The water she ingested distributed to maintain osmotic equilibrium, so water entered the ICF from the ECF, resulting in cell swelling.</td>
</tr>
</tbody>
</table>
### Question 5
In dilutional hyponatremia, the medical personnel are most concerned about which organ or tissue?

- All cells in Lauren’s body swell as a result of excess water ingestion. The brain is encased in the rigid skull.

### Integration and Analysis
The bony skull restricts the swelling of brain tissue, causing neurological symptoms, including confusion, headache, and loss of coordination. With lower Na⁺ concentrations, death can result.

### Question 6
Assuming a sweating rate of 1.0 L/hr, how much Na⁺ did Lauren lose during the 16-hour race?

- 1.0 L sweat lost/hr × 16 hr × 70 mEq Na⁺/L sweat = 1120 mEq Na⁺ lost during the 16-hour race.

### Integration and Analysis
Lauren must have ingested at least 18 liters of fluid. You have no information on other routes of fluid loss, such as urine and insensible water lost during breathing.

### Question 7
Total body water for a 60-kg female is approximately 30 L, and her ECF volume is 10 L. Based on the information given so far, how much fluid did Lauren ingest during the race?

From the sweating rate given in question 6, you know that Lauren lost 16 liters of sweat during the race. You also know that she gained 2 kg in weight. One liter of water weighs 1 kg.

### Integration and Analysis
Lauren must have ingested at least 18 liters of fluid. You have no information on other routes of fluid loss, such as urine and insensible water lost during breathing.

### Question 8
What would you expect to happen to vasopressin and aldosterone production in response to dilutional hyponatremia?

- Vasopressin secretion is inhibited by a decrease in osmolarity. The usual stimuli for renin or aldosterone release are low blood pressure and hyperkalemia.

### Integration and Analysis
Vasopressin secretion decreases with hyponatremia. The usual stimuli for aldosterone secretion are absent, but a pathological decrease in plasma Na⁺ of 10 mEq/L can stimulate the adrenal cortex to secrete aldosterone. Thus, Lauren’s plasma Na⁺ may be low enough to increase her aldosterone secretion.

*N/A = not applicable

This problem was developed by Matt Pahnke while he was a kinesiology graduate student at the University of Texas.
Fluid and Electrolyte Homeostasis

1. The renal, respiratory, and cardiovascular systems control fluid and electrolyte balance. Behaviors such as drinking also play an important role. (Fig. 20.1)
2. Pulmonary and cardiovascular compensations are more rapid than renal compensation.

Water Balance

Urinary: Early Filtrate Processing

3. Most water intake comes from food and drink. The largest water loss is 1.5 liters/day in urine. Smaller amounts are lost in feces, by evaporation from skin, and in exhaled humidified air. (Fig. 20.2)
4. Renal water reabsorption conserves water but cannot restore water lost from the body. (Fig. 20.3)
5. To produce dilute urine, the nephron must reabsorb solute without reabsorbing water. To concentrate urine, the nephron must reabsorb water without reabsorbing solute.
6. Filtrate leaving the ascending limb of the loop of Henle is dilute. The final concentration of urine depends on the water permeability of the collecting duct. (Fig. 20.4)
7. The hypothalamic hormone vasopressin controls collecting duct permeability to water in a graded fashion. When vasopressin is absent, water permeability is nearly zero. (Fig. 20.5, 20.6)
8. Vasopressin causes distal nephron cells to insert aquaporin water pores in their apical membrane. (Fig. 20.5)
9. An increase in ECF osmolarity or a decrease in blood pressure stimulates vasopressin release from the posterior pituitary. Osmolarity is monitored by hypothalamic osmoreceptors. Blood pressure and blood volume are sensed by receptors in the carotid and aortic bodies, and in the atria, respectively. (Fig. 20.6)
10. The loop of Henle is a countercurrent multiplier that creates high osmolarity in the medullary interstitial fluid by actively transporting Na⁺, Cl⁻, and K⁺ out of the nephron. This high medullary osmolarity is necessary for formation of concentrated urine as filtrate flows through the collecting duct. (Fig. 20.7)
11. The vasa recta capillaries is a countercurrent exchanger that carries away water leaving the tubule so that the water does not dilute the medullary interstitium. (Fig. 20.7)
12. Urea contributes to the high osmolarity in the renal medulla.

Sodium Balance and ECF Volume

Urinary: Late Filtrate Processing

13. The total amount of Na⁺ in the body is a primary determinant of ECF volume. (Fig. 20.8)
14. The steroid hormone aldosterone increases Na⁺ reabsorption and K⁺ secretion. (Fig. 20.9a)
15. Aldosterone acts on principal cells (P cells) of the distal nephron. This hormone enhances Na⁺-K⁺-ATPase activity and increases open time of Na⁺ and K⁺ leak channels. It also stimulates the synthesis of new pumps and channels. (Fig. 20.9b)
16. Aldosterone secretion can be controlled directly at the adrenal cortex. Increased ECF K⁺ stimulates aldosterone secretion, but very high ECF osmolarity inhibits it. (Fig. 20.9)
17. Aldosterone secretion is also stimulated by angiotensin II. Granular cells in the kidney secrete renin, which converts angiotensinogen in the blood to angiotensin I. Angiotensin-converting enzyme (ACE) converts ANG I to ANG II. (Fig. 20.10)
18. The stimuli for the release of renin are related either directly or indirectly to low blood pressure. (Fig. 20.10)
19. ANG II has additional effects that raise blood pressure, including increased vasopressin secretion, stimulation of thirst, vasconstriction, and activation of the cardiovascular control center. (Fig. 20.10)
20. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) enhance Na⁺ excretion and urinary water loss by increasing GFR, inhibiting tubular reabsorption of NaCl, and inhibiting the release of renin, aldosterone, and vasopressin. (Fig. 20.11)

Potassium Balance

21. Potassium homeostasis keeps plasma K⁺ concentrations in a narrow range. Hyperkalemia and hypokalemia cause problems with excitable tissues, especially the heart.

Behavioral Mechanisms in Salt and Water Balance

22. Thirst is triggered by hypothalamic osmoreceptors and relieved by drinking.
23. Salt appetite is triggered by aldosterone and angiotensin.

Integrated Control of Volume and Osmolarity

Fluids & Electrolytes: Water Homeostasis

24. Homeostatic compensations for changes in salt and water balance follow the law of mass balance. Fluid and solute added to the body must be removed, and fluid and solute lost from the body must be replaced. However, perfect compensation is not always possible. (Tb. 20.1)

Acid-Base Balance

25. The body’s pH is closely regulated because pH affects intracellular proteins, such as enzymes and membrane channels.
26. Acid intake from foods and acid production by the body’s metabolic processes are the biggest challenge to body pH. The most significant source of acid is CO₂ from respiration, which combines with water to form carbonic acid (H₂CO₃). (Fig. 20.14)
27. The body copes with changes in pH by using buffers, ventilation, and renal secretion or reabsorption of H⁺ and HCO₃⁻. (Fig. 20.14)
28. Bicarbonate produced from CO₂ is the most important extracellular buffer of the body. Bicarbonate buffers organic acids produced by metabolism.
29. Ventilation can correct disturbances in acid-base balance because changes in plasma P₅₀ affect both the H⁺ content and the HCO₃⁻ content of the blood. An increase in P₅₀ stimulates central chemoreceptors. An increase in plasma H⁺ stimulates carotid and aortic chemoreceptors. Increased ventilation excretes CO₂ and decreases plasma H⁺. (Fig. 20.15)
30. In acidosis, the kidneys secrete H⁺ and reabsorb HCO₃⁻. (Figs. 20.16, 20.17b)
31. In alkalosis, the kidneys secrete HCO₃⁻ and reabsorb H⁺. (Fig. 20.17c)
32. Intercalated cells in the collecting duct are responsible for the fine regulation of acid-base balance. (Fig. 20.17b, c)
Questions

Level One  Reviewing Facts and Terms
1. What is an electrolyte? Name five electrolytes whose concentrations must be regulated by the body.
2. List five organs and four hormones important in maintaining fluid and electrolyte balance.
3. Compare the routes by which water enters the body with the routes by which the body loses water.
4. List the receptors that regulate osmolarity, blood volume, blood pressure, ventilation, and pH. Where are they located, what stimulates them, and what compensatory mechanisms are triggered by them?
5. How do the two limbs of the loop of Henle differ in their permeability to water? What makes this difference in permeability possible?
6. Which ion is a primary determinant of ECF volume? Which ion is the determinant of extracellular pH?
7. What happens to the resting membrane potential of excitable cells when plasma K⁺ concentrations decrease? Which organ is most likely to be affected by changes in K⁺ concentration?
8. Appetite for what two substances is important in regulating fluid volume and osmolarity?
9. Write out the words for the following abbreviations: ADH, ANP, ACE, ANG II, JG apparatus, P cell, I cell.
10. Make a list of all the different membrane transporters in the kidney. For each transporter, tell (a) which section(s) of the nephron contains the transporter; (b) whether the transporter is on the apical membrane only, on the basolateral membrane only, or on both; (c) whether it participates in reabsorption only, or secretion only, or in both.
11. List and briefly explain three reasons why monitoring and regulating ECF pH are important. What three mechanisms does the body use to cope with changing pH?
12. Which is more likely to accumulate in the body, acids or bases? List some sources of each.
13. What is a buffer? List three intracellular buffers. Name the primary extracellular buffer.
14. Name two ways the kidneys alter plasma pH. Which compounds serve as urinary buffers?
15. Write the equation that shows how CO₂ is related to pH. What enzyme increases the rate of this reaction? Name two cell types that possess high concentrations of this enzyme.
16. When ventilation increases, what happens to arterial P₃CO₂? To plasma pH? To plasma H⁺ concentration?

Level Two  Reviewing Concepts
17. Concept map: Map the homeostatic reflexes that occur in response to each of the following situations:
   (a) decreased blood volume, normal blood osmolarity
   (b) increased blood volume, increased blood osmolarity
   (c) normal blood volume, increased blood osmolarity
18. Figures 20.15 and 20.17b show the respiratory and renal compensations for acidosis. Draw similar maps for alkalosis.
19. Explain how the loop of Henle and vasa recta work together to create dilute renal filtrate.
20. Diagram the mechanism by which vasopressin alters the composition of urine.
21. Make a table that specifies the following for each substance listed: hormone or enzyme? steroid or peptide? produced by which cell or tissue? target cell or tissue? target has what response?
   (a) ANP
   (b) aldosterone
   (c) renin
   (d) ANG II
   (e) vasopressin
   (f) angiotensin-converting enzyme
22. Name the four main compensatory mechanisms for restoring low blood pressure to normal. Why do you think there are so many homeostatic pathways for raising low blood pressure?
23. Compare and contrast the terms in each set:
   (a) principal cells and intercalated cells
   (b) renin, ANG II, aldosterone, ACE
   (c) respiratory acidosis and metabolic acidosis, including causes and compensations
   (d) water reabsorption in proximal tubule, distal tubule, and ascending limb of the loop of Henle
   (e) respiratory alkalosis and metabolic alkalosis, including causes and compensations
24. The interstitial fluid in contact with the basolateral side of collecting duct cells has an extremely high osmolarity, and yet the cells do not shrivel up. How can they maintain normal cell volume in the face of such high ECF osmolarity?

Level Three  Problem Solving
25. A 45-year-old man visiting from out of town arrives at the emergency room having an asthma attack caused by pollen.
   (a) Blood drawn before treatment showed the following: HCO₃⁻ = 30 meq/L (normal: 24), P₃CO₂ = 70 mm Hg, pH = 7.24. What is the man’s acid-base state? Is this an acute or a chronic situation?
   (b) The man was treated and made a complete recovery. Over the next ten years he continued to smoke a pack of cigarettes a day, and a year ago his family doctor diagnosed chronic obstructive pulmonary disease (emphysema). The man’s most recent blood test showed the following: HCO₃⁻ = 45 meq/L, P₃CO₂ = 85 mm Hg, pH = 7.34. What is the man’s acid-base state now? Is this an acute or a chronic situation?
   (c) Explain why in his second illness his plasma bicarbonate level and P₃CO₂ are higher than in the first illness but his pH is closer to normal.
26. The U.S. Food and Drug Administration recently approved a new class of drugs called vasopressin receptor antagonists. Predict the effect these drugs would have on renal function and describe some clinical situations or diseases in which these drugs might be useful.
27. Karen has bulimia, in which she induces vomiting to avoid weight gain. When the doctor sees her, her weight is 89 lb and her respiratory rate is 6 breaths/min (normal 12). Her blood HCO₃⁻ is 62 meq/L (normal: 24–29), arterial blood pH is 7.61, and P₃CO₂ is 61 mm Hg.
   (a) What is her acid-base condition called?
   (b) Explain why her plasma bicarbonate level is so high.
   (c) Why is she hyperventilating? What effect does this have on the pH and total oxygen content of her blood? Explain your answers.
28. Hannah, a 31-year-old woman, decided to have colonic irrigation, a procedure during which large volumes of distilled water were infused into her rectum. During the treatment she absorbed 3000 mL
of water. About 12 hours later, her roommate found her in convulsions and took her to the emergency room. Her blood pressure was 140/90, her plasma Na⁺ concentration was 106 meq/L (normal: 135 meq/L), and her plasma osmolarity was 270 mOsM. In a concept map or flow chart, diagram all the homeostatic responses her body was using to attempt compensation for the changes in blood pressure and osmolarity.

**Level Four Quantitative Problems**

29. The Henderson-Hasselbalch equation is a mathematical expression of the relationship between pH, HCO₃⁻ concentration, and dissolved CO₂ concentration. One variant of the equation uses P₀₂ instead of dissolved CO₂ concentration:

\[
\text{pH} = 6.1 + \log \left[ \text{HCO}_3^- \right] / 0.03 \times P_{CO_2}
\]

(a) If arterial blood has a P₀₂ of 40 mm Hg and its HCO₃⁻ concentration is 24 mM, what is its pH? (Use a log table or calculator with a logarithmic function capability.)

(b) What is the pH of venous blood with the same HCO₃⁻ concentration but a P₀₂ of 46 mm Hg?

30. In extreme dehydration, urine can reach a concentration of 1400 mOsM. If the minimum amount of waste solute that a person must excrete daily is about 600 milliosmoles, what is the minimum urine volume that is excreted in one day?

31. Hyperglycemia in a diabetic patient leads to osmotic diuresis and dehydration. Given the following information, answer the questions.

Plasma glucose = 400 mg/dL
Normal urine flow = 1 L per day
GFR = 130 mL/min
Normal urine osmolarity = 300 mOsM
Glucose T₉₀ = 400 mg/min
Molecular mass of glucose = 180 dalton
Renal plasma flow = 500 mL/min
(a) How much glucose filters into the nephron each minute?
(b) How much glucose is reabsorbed each minute?
(c) How much glucose is excreted in the urine each day?
(d) Assuming that dehydration causes maximal vasopressin secretion and allows the urine to concentrate to 1200 mOsM, how much additional urine does this diabetic patient excrete in a day?

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**Answers to Concept Check Questions**

1. Apical membranes have more water pores when vasopressin is present.

2. If vasopressin secretion is suppressed, the urine is dilute.

3. Hyperosmotic NaCl is hypertonic and causes the osmoreceptors to shrink, but hyperosmotic urea is hypotonic and causes them to swell. Because only cell shrinkage causes firing, osmoreceptors exposed to urea do not fire.

4. Because vasopressin enhances water reabsorption, vasopressin levels would increase with dehydration.

5. Osmoreceptors in the lumen of the digestive tract and hepatic portal vein would sense high-osmolarity food or drink that has been ingested and absorbed, before it is in the general circulation. This would allow an anticipatory, or feed-forward, secretion of vasopressin to conserve body water.

6. Solutes that remain in the lumen when the NKCC symporter is inhibited force water to remain in the lumen with them because urine can be concentrated only to 1200 mOsM. Thus each 12 millimoles of un-reabsorbed solute “holds” an additional 10 mL of water in the urine.

7. Diuretics that inhibit the NKCC symporter leave K⁺ in the tubule lumen, where it is likely to be excreted, thus increasing urinary K⁺ loss.

8. Na⁺ and K⁺ are moving down their electrochemical gradients.

9. In hyperkalemia, resting membrane potential depolarizes. Excitable tissues fire one action potential but are unable to repolarize to fire a second one.

10. Atherosclerotic plaques block blood flow, which decreases GFR and decreases pressure in the afferent arteriole. Both events are stimuli for renin release.

11. Renin secretion begins a cascade that produces ANG II. This powerful hormone then causes vasoconstriction, acts on the medullary cardiovascular control center to increase blood pressure, increases production of vasopressin and aldosterone, and increases thirst, resulting in drinking and an increased fluid volume in the body. All these responses may contribute to increased blood pressure.

12. All blood passes through the pulmonary blood vessels with each circuit. Unless ACE was in every systemic blood vessel, some blood might not be exposed to ACE every time.

13. On the left side of Figure 20.8, interneurons also lead from hypothalamic osmoreceptors to the hypothalamic thirst centers.

14. The bicarbonate level increases as the reaction shifts to the right as a result of added CO₂. Once a new equilibrium state is achieved, bicarbonate cannot act as a buffer because the system is at equilibrium.

15. In the distal nephron, both K⁺ and H⁺ are being moved against their concentration gradients, which requires ATP. In the proximal tubule, Na⁺ is moving down its concentration gradient, providing the energy to push H⁺ against its gradient.

16. When intercalated cells reabsorb K⁺, they secrete H⁺, and therefore blood pH increases.
Integrative Physiology II: Fluid and Electrolyte Balance

Answers to Figure Questions

Figure 20.6: 1. Threshold is 280 mOsm. 2. An action potential arriving at the axon terminal initiates exocytosis. Figure 20.8.

Figure 20.10 Figure 20.9b for the target cell involved in aldosterone action, and Figure 20.5c for the target cell involved in vasopressin action. Figure 20.15: The muscles of inspiration are the diaphragm, the external intercostals, the scalenes, and sternocleidomastoid. Muscles of expiration are the abdominals and internal intercostals.

Answers to Review Questions

Level One  Reviewing Facts and Terms
1. Electrolytes are ions, which can conduct electric current through a solution. Examples: Na⁺, K⁺, Ca²⁺, H⁺, HPO₄²⁻, and HCO₃⁻.
2. Organs: kidneys, lungs, heart, blood vessels, digestive tract. Hormones: vasopressin (ADH), aldosterone, atrial natriuretic peptides (ANP), RAS pathway.
3. Entry: ingested and a small amount from metabolism. Loss: exhaled air, evaporation and perspiration from skin, excreted by kidneys, and in feces.
4. See Table 20.1 and Figure 20.15.
5. Descending limb: permeable to water but lacks transporters for salts. Ascending limb: impermeable to water but reabsorbs NaCl.
6. ECF volume—Na⁺; pH — H⁺
7. More K⁺ leaves the cell, and membrane potential becomes more negative (hyperpolarizes). The heart is most likely to be affected.
8. Salt and water
9. ADH = antidiuretic hormone; ANP = atrial natriuretic peptide; ACE = angiotensin-converting enzyme; ANG II = angiotensin II; JG (apparatus) = juxtaglomerular; P cell = principal cell; I cell = intercalated cell.
10. Use Figures 20.5b, 20.7d, 20.9, and 20.17.
12. Acids from CO₂, metabolism, and food are more likely. Sources of bases include some foods.
14. Kidneys excrete or reabsorb H⁺ or HCO₃⁻. Ammonia and phosphates.
15. CO₂ + H₂O → H₂CO₃ → H⁺ + HCO₃⁻. Carbonic anhydrase. High in renal tubule cells and RBCs.
16. Arterial P CO₂ decreases, pH increases, and plasma H⁺ concentration decreases.

Level Two  Reviewing Concepts
17. Use the information in Table 20.1 and compile multiple pathways into a single map similar to Figure 20.13. Include all steps of the reflex.
18. Combine information from Figures 20.15 and 20.17c.
19. See Figure 20.7.
20. See Figure 20.6.
21. (a) ANP—peptide from atrial myocardial cells. Causes Na⁺ and water excretion; inhibits ADH secretion. (b) Aldosterone—steroid from adrenal cortex. Increases distal nephron Na⁺ reabsorption and K⁺ excretion. (c) Renin—enzyme from JG cells. Converts plasma angiotensinogen to ANG I. (d) ANG II—peptide hormone made from ANG I. Increases blood pressure by actions on arterioles, brain, and adrenal cortex. (e) Vasopressin—hypothalamic peptide. Increases distal nephron water reabsorption. (f) ACE—enzyme on vascular endothelium. Converts ANG I to ANG II.

22. Vasocostriction, increased cardiac output, water conservation by kidneys, and increased thirst. If blood pressure falls too low, oxygen supply to the brain will decrease, resulting in damage or death.
23. (a) Both are in the distal nephron. P cells are associated with aldosterone-mediated Na⁺ reabsorption; I cells are involved with acid-base regulation. (b) All are parts of the RAS system. Renin and ACE—enzymes; ANG II and aldosterone—hormones. See Figure 20.10. (c) In both, body pH falls below 7.38. Respiratory—results from CO₂ retention (from any number of causes); metabolic—results from excessive production of metabolic acids. Respiratory compensation—renal H⁺ excretion and HCO₃⁻ retention. Metabolic compensation—increased ventilation, renal H⁺ excretion, and HCO₃⁻ retention. Respiratory—arterial P CO₂ is elevated; metabolic—P CO₂ usually decreased. (d) Proximal tubule—not regulated; distal nephron—regulated by vasopressin. Ascending limb—impermeable to water. (e) Both—pH goes above 7.42. Metabolic—may be caused by excessive ingestion of bicarbonate-containing antacids or vomiting; respiratory—hyperventilation. Metabolic compensation—decrease ventilation, decreased renal H⁺ excretion, increased HCO₃⁻ excretion. Respiratory compensation—decreased renal H⁺ excretion, increased HCO₃⁻ excretion.
24. The cells concentrate organic solutes to increase their internal osmolarity.

Level Three  Problem Solving
25. (a) Acute respiratory acidosis (b) Chronic respiratory acidosis (c) Renal compensation has increased his pH by H⁺ excretion and HCO₃⁻ reabsorption. His P CO₂ is elevated because of his emphysema.
26. These drugs decrease ADH-mediated water reabsorption. Useful in people who secrete too much vasopressin (SIADH, or syndrome of inappropriate ADH secretion) or in hyponatremia, such as the woman in this chapter’s Running Problem.
27. (a) Metabolic alkalosis, partially compensated. (b) After vomiting acid (H⁺), her body was left with HCO₃⁻. (c) Hypoventilation increases P CO₂, HCO₃⁻, and H⁺. Increased H⁺ decreases pH (compensation). Hypoventilation also decreases arterial P O₂, and decreases the total oxygen content of blood.
28. Blood pressure is high, plasma Na⁺ and osmolarity are low. Use Table 20.1 to select reflex pathways for the map.

Level Four  Quantitative Problems
29. (a) pH = 6.1 + log ([24/(0.03 × 40)] = 7.40 (b) 7.34
30. 428.6 mL (600 mosmol/L = 1400 mosmol/L)
31. (a) 400 mg glucose/100 mL × 130 mL/min = 520 mg glucose/min filters. (b) Can reabsorb up to T m, so 400 mg/min reabsorbed. (c) Excreted = filtered − reabsorbed = 120 mg/min × 1440 min/day = 172.8 g/day excreted. (d) Convert grams to millimoles: 172.8 g × mole/180 g × 1000 mosmol/mole = 960 mosmol glucose excreted/day. Concentration = amount/volume. 1200 mosmol/L = 960 mosmol/L² liters. Will require 0.8 L additional volume.

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