CHAPTER 24

Water, Electrolyte, and Acid-Base Balance

Two glomeruli (*green*) and renal tubules (*violet*) of the kidney

CHAPTER OUTLINE

INSIGHTS

Brushing Up

To understand this chapter, it is important that you understand or brush up on the following concepts:
- Electrolytes and milliequivalents/liter (p. 67)
- Acids, bases, and the pH scale (p. 67)
- Osmolarity (p. 108)
- Role of electrolytes in plasma membrane potentials (pp. 455–456)
- Depolarization and hyperpolarization of plasma membranes (fig. 12.21, p. 469)
- The hypothalamus and posterior pituitary (p. 637)
- Influence of CO_2 and pH on pulmonary ventilation (pp. 867–868)
- Structure and physiology of the nephron (pp. 882–896)

Cellular function requires a fluid medium with a carefully controlled composition. If the quantity, osmolarity, electrolyte concentration, or pH of this medium is altered, life-threatening disorders of cellular function may result. Consequently, the body has several mechanisms for keeping these variables within narrow limits and maintaining three types of homeostatic balance:

1. *water balance,* in which average daily water intake and loss are equal;
2. *electrolyte balance,* in which the amount of electrolytes absorbed by the small intestine balance the amount lost from the body, chiefly through the urine; and
3. *acid-base balance,* in which the body rids itself of acid (hydrogen ions) at a rate that balances its metabolic production, thus maintaining a stable pH.

These balances are maintained by the collective action of the urinary, respiratory, digestive, integumentary, endocrine, nervous, cardiovascular, and lymphatic systems. This chapter describes the homeostatic regulation of water, electrolyte, and acid-base balance and shows the close relationship of these variables to each other.

Water Balance

Objectives
When you have completed this section, you should be able to
- name the major fluid compartments and explain how water moves from one to another;
- list the body's sources of water and routes of water loss;
- describe the mechanisms of regulating water intake and output; and
- describe some conditions in which the body has a deficiency or excess of water or an improper distribution of water among the fluid compartments.

We enter the world in a rather soggy condition, having swallowed, excreted, and floated in amniotic fluid for months. At birth, a baby's weight is as much as 75% water; infants normally lose a little weight in the first day or two as they excrete the excess. Young adult men average 55% to 60% water, while women average slightly less because they have more adipose tissue, which is nearly free of water. Obese and elderly people are as little as 45% water by weight. The **total body water (TBW)** content of a 70 kg (150 lb) young male is about 40 L.

Fluid Compartments

Body water is distributed among the following **fluid compartments,** which are separated by selectively permeable membranes and differ from each other in chemical composition:

65% *intracellular fluid (ICF)* and
35% *extracellular fluid (ECF),* subdivided into
    25% *tissue (interstitial) fluid,*
    8% *blood plasma* and *lymph,* and
    2% *transcellular fluid,* a catch-all category for cerebrospinal, synovial, peritoneal, pleural, and pericardial fluids; vitreous and aqueous humors of the eye; bile; and fluid in the digestive, urinary, and respiratory tracts.

Fluid is continually exchanged between compartments by way of capillary walls and plasma membranes (fig. 24.1). Water moves by osmosis from the digestive tract to the bloodstream and by capillary filtration from the blood to the tissue fluid. From the tissue fluid, it may be reabsorbed by the capillaries, osmotically absorbed into cells, or taken up by the lymphatic system, which returns it to the bloodstream.

Because water moves so easily through plasma membranes, osmotic gradients between the ICF and ECF never last for very long. If a local imbalance arises, osmosis usually restores the balance within seconds so that intracellular and extracellular osmolarity are equal. If the osmolarity of the tissue fluid rises, water moves out of the cells; if it falls, water moves into the cells.

Osmosis from one fluid compartment to another is determined by the relative concentration of solutes in each compartment. The most abundant solute particles by far are the electrolytes—especially sodium salts in the ECF and potassium salts in the ICF. Electrolytes play the principal role in governing the body's water distribution and total water content; the subjects of water and electrolyte balance are therefore inseparable.

Water Gain and Loss

A person is in a state of **water balance** when daily gains and losses are equal. We typically gain and lose about 2,500 mL/day (fig. 24.2). The gains come from two sources: **metabolic water** (about 200 mL/day), which is produced as a by-product of aerobic respiration and dehydration synthesis reactions, and **preformed water,** which is ingested in food (700 mL/day) and drink (1,600 mL/day).

The routes of water loss are more varied:

- 1,500 mL/day is excreted as urine.

- 200 mL/day is eliminated in the feces.

- 300 mL/day is lost in the expired breath. You can easily visualize this by breathing onto a cool surface such as a mirror.

- 100 mL/day of sweat is secreted by a resting adult at an ambient (air) temperature of 20°C (68°F).
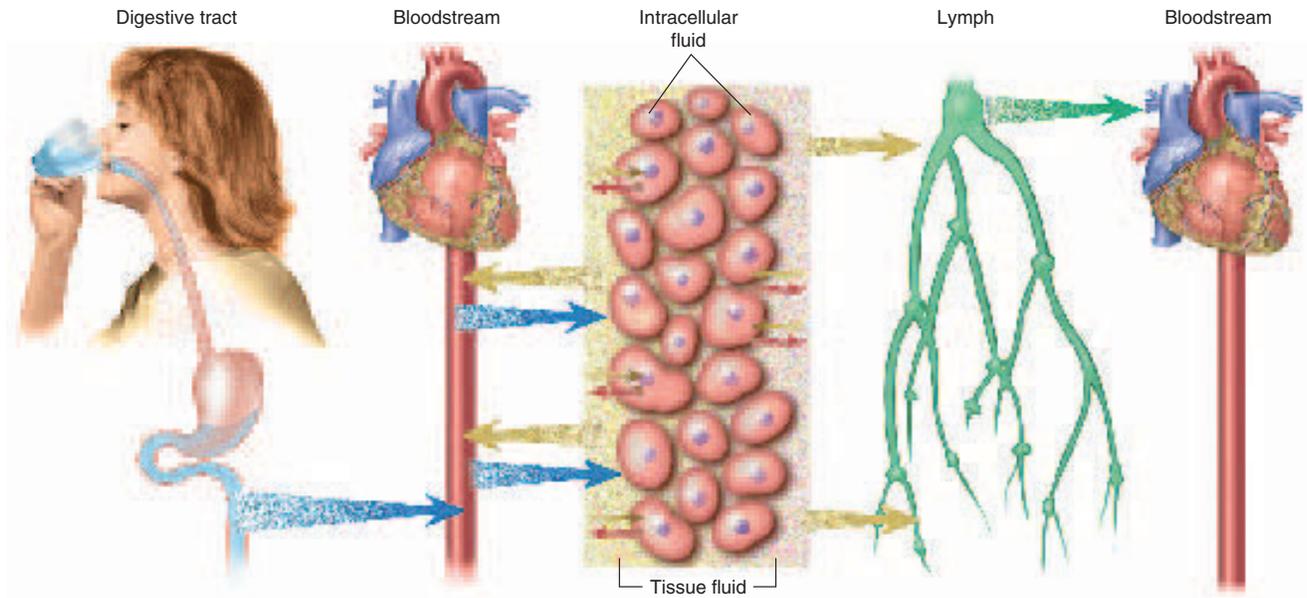
Digestive tract   Bloodstream   Intracellular fluid   Lymph   Bloodstream

└ Tissue fluid ┘

Figure 24.1 **The Movement of Water Between the Major Fluid Compartments.** Ingested water is absorbed by the bloodstream. There is a two-way exchange of water between the blood and tissue fluid and between the tissue and intracellular fluids. Excess tissue fluid is picked up by the lymphatic system, which returns it to the bloodstream.
In which of these places would fluid accumulate in edema?

- 400 mL/day is lost as **cutaneous transpiration,**[1] water that diffuses through the epidermis and evaporates. This is not the same as sweat; it is not a glandular secretion. A simple way to observe it is to cup the palm of your hand for a minute against a cool nonporous surface such as a laboratory benchtop or mirror. When you take your hand away, you will notice the water that transpired through the skin and condensed on that surface.

Water loss varies greatly with physical activity and environmental conditions. Respiratory loss increases in cold weather, for example, because cold air is drier and absorbs more body water from the respiratory tract. Hot, humid weather slightly reduces the respiratory loss but increases perspiration to as much as 1,200 mL/day. Prolonged, heavy work can raise the respiratory loss to 650 mL/day and perspiration to as much as 5 L/day, though it reduces urine output by nearly two-thirds.

Output through the breath and cutaneous transpiration is called **insensible water loss** because we are not usually conscious of it. **Obligatory water loss** is output that is relatively unavoidable: expired air, cutaneous transpiration, sweat, fecal moisture, and the minimum urine out-

put, about 400 mL/day, needed to prevent azotemia. Even dehydrated individuals cannot prevent such losses; thus they become further dehydrated.

Regulation of Intake

Fluid intake is governed mainly by thirst, which is controlled by the mechanisms shown in figure 24.3. Dehydration reduces blood volume and pressure and raises blood osmolarity. The hypothalamus has a nucleus called the **thirst center** that responds to multiple signs of dehydration: (1) angiotensin II, produced in response to falling blood pressure; (2) antidiuretic hormone, released in response to rising blood osmolarity; and (3) signals from *osmoreceptors,* neurons in the hypothalamus that monitor the osmolarity of the ECF. A 2% to 3% increase in plasma osmolarity makes a person intensely thirsty, as does a 10% to 15% blood loss.

In response to such cues, the thirst center sends sympathetic signals to the salivary glands to inhibit salivation. Salivation is also reduced for another reason. Most of the saliva is produced by capillary filtration, but in dehydration, filtration is reduced by the lower blood pressure and higher osmolarity of the blood. Reduced salivation gives us a dry, sticky-feeling mouth, but it is by no means certain that this is our primary motivation to drink. People who do not secrete saliva and experimental animals that

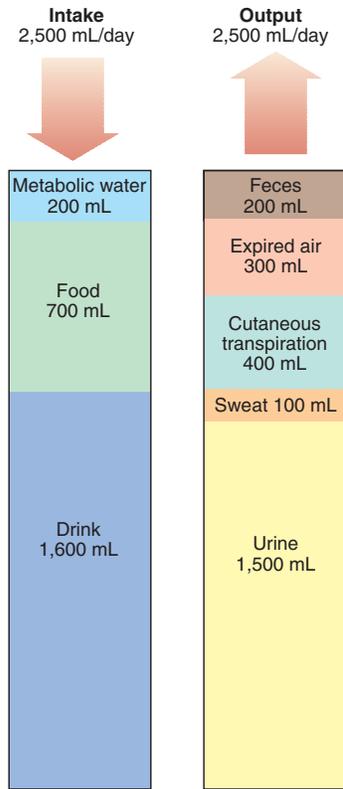[1]*trans* = across, through + *spir* = to breathe

Figure 24.2 Typical Water Intake and Output in a State of Fluid Balance.

Figure 24.3 Dehydration, Thirst, and Rehydration.

have the salivary ducts tied off do not drink any more than normal individuals except when eating, when they need water to moisten the food.

Long-term satiation of thirst depends on absorbing water from the small intestine and lowering the osmolarity of the blood. Reduced osmolarity stops the osmoreceptor response, promotes capillary filtration, and makes the saliva more abundant and watery. However, these changes require 30 minutes or longer to take effect, and it would be rather impractical if we had to drink that long while waiting to feel satisfied. Water intake would be grossly excessive. Fortunately, there are mechanisms that act more quickly to temporarily quench the thirst and allow time for the change in blood osmolarity to occur.

Experiments with rats and dogs have isolated the stimuli that quench the thirst. One of these is cooling and moistening the mouth; rats drink less if their water is cool than if it is warm, and simply moistening the mouth temporarily satisfies an animal even if the water is drained from its esophagus before it reaches the stomach. Distension of the stomach and small intestine is another inhibitor of thirst. If a dog is allowed to drink while the wat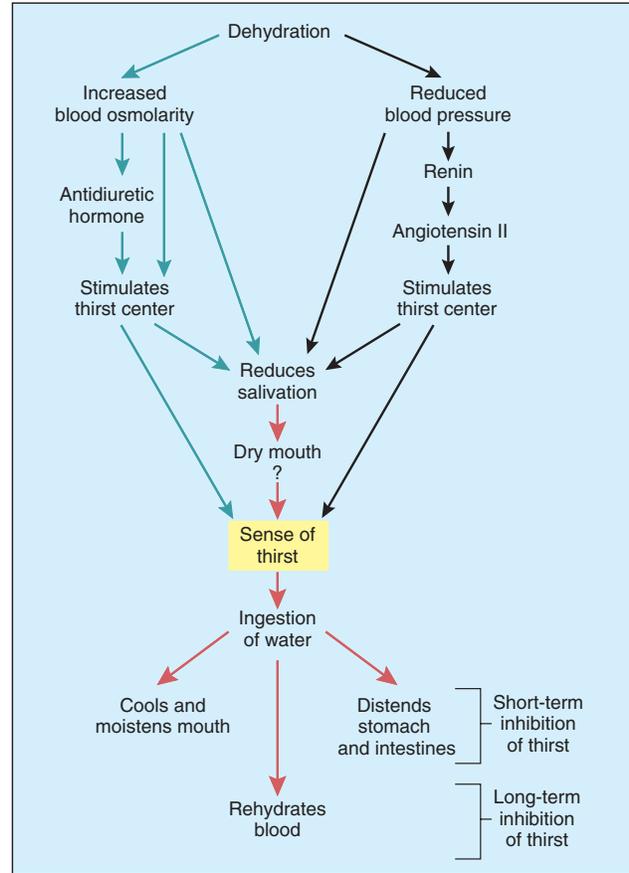er is drained from its esophagus but its stomach is inflated with a balloon, its thirst is satisfied for a time. If the water is drained away but the stomach is not inflated, satiation does not last as long. Such fast-acting stimuli as coolness, moisture, and filling of the stomach stop an animal (and presumably a human) from drinking an excessive amount of liquid, but they are effective for only 30 to 45 minutes. If they are not soon followed by absorption of water into the bloodstream, the thirst soon returns. Only a drop in blood osmolarity produces a lasting effect.

Regulation of Output

The only way to control water output significantly is through variations in urine volume. It must be realized, however, that the kidneys cannot completely prevent water loss, nor can they replace lost water or electrolytes. Therefore, they never restore fluid volume or osmolarity, but in dehydration they can support existing fluid levels and slow down the rate of loss until water and electrolytes are ingested.

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To understand the effect of the kidneys on water and electrolyte balance, it is also important to bear in mind that if a substance is reabsorbed by the kidneys, it is kept in the body and returned to the ECF, where it will affect fluid volume and composition. If a substance is filtered by the glomerulus or secreted by the renal tubules and not reabsorbed, then it is excreted in the urine and lost from the body fluids.

Changes in urine volume are usually linked to adjustments in sodium reabsorption. As sodium is reabsorbed or excreted, proportionate amounts of water accompany it. The total volume of fluid remaining in the body may change, but its osmolarity remains stable. Controlling water balance by controlling sodium excretion is best understood in the context of electrolyte balance, discussed later in the chapter.

Antidiuretic hormone (ADH), however, provides a means of controlling water output independently of sodium. In true dehydration (defined shortly), blood volume declines and sodium concentration rises. The increased osmolarity of the blood stimulates the hypothalamic osmoreceptors, which stimulate the posterior pituitary to release ADH. In response to ADH, cells of the collecting ducts of the kidneys synthesize the proteins called aquaporins. When installed in the plasma membrane, these serve as channels that allow water to diffuse out of the duct into the hypertonic tissue fluid of the renal medulla. Thus the kidneys reabsorb more water and produce less urine. Sodium continues to be excreted, so the *ratio* of sodium to water in the urine increases (the urine becomes more concentrated). By helping the kidneys retain water, ADH slows down the decline in blood volume and the rise in its osmolarity. Thus the ADH mechanism forms a negative feedback loop (fig. 24.4).

Conversely, if blood volume and pressure are too high or blood osmolarity is too low, ADH release is inhibited. The renal tubules reabsorb less water, urine output increases, and total body water declines. This is an effective way of compensating for hypertension. Since the lack of ADH increases the ratio of water to sodium in the urine, it raises the sodium concentration and osmolarity of the blood.

Disorders of Water Balance

The body is in a state of fluid imbalance if there is an abnormality of total fluid *volume,* fluid *concentration,* or fluid *distribution* among the compartments.

Fluid Deficiency

Fluid deficiency arises when output exceeds intake over a long period of time. There are two kinds of deficiency, called volume depletion and dehydration, which differ in the relative loss of water and electrolytes and the resulting osmolarity of the ECF. This is an important distinction that
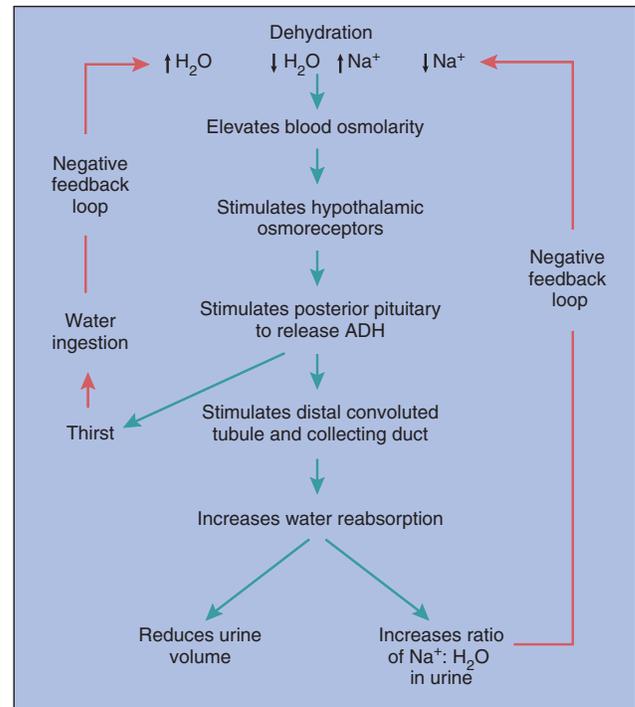

Figure 24.4 The Secretion and Effects of Antidiuretic Hormone. Pathways shown in *red* represent negative feedback.

calls for different strategies of fluid replacement therapy (see insight 24.2 at the end of the chapter).

Volume depletion (hypovolemia[2]) occurs when proportionate amounts of water *and* sodium are lost without replacement. Total body water declines but osmolarity remains normal. Volume depletion occurs in cases of hemorrhage, severe burns, and chronic vomiting or diarrhea. A less common cause is aldosterone hyposecretion (Addison disease), which results in inadequate sodium and water reabsorption.

Dehydration (negative water balance) occurs when the body eliminates significantly more water than sodium, so the ECF osmolarity rises. The simplest cause of dehydration is a lack of drinking water; for example, when stranded in a desert or at sea. It can be a serious problem for elderly and bedridden people who depend on others to provide them with water—especially for those who cannot express their need or whose caretakers are insensitive to it. Diabetes mellitus, ADH hyposecretion (diabetes insipidus), profuse sweating, and overuse of diuretics are additional causes of dehydration. Prolonged exposure to cold weather can dehydrate a person just as much as exposure to hot weather (see insight 24.1).

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[2]*hypo* = below normal + *vol* = volume + *emia* = blood condition

For three reasons, infants are more vulnerable to dehydration than adults: (1) Their high metabolic rate produces toxic metabolites faster, and they must excrete more water to eliminate them. (2) Their kidneys are not fully mature and cannot concentrate urine as effectively. (3) They have a greater ratio of body surface to volume; consequently, compared to adults, they lose twice as much water per kilogram of body weight by evaporation.

Dehydration affects all fluid compartments. Suppose, for example, that you play a strenuous tennis match on a hot summer day and lose a liter of sweat per hour. Where does this fluid come from? Most of it filters out of the bloodstream through the capillaries of the sweat glands. In principle, 1 L of sweat would amount to about one-third of the blood plasma. However, as the blood loses water its osmolarity rises and water from the tissue fluid enters the bloodstream to balance the loss. This raises the osmolarity of the tissue fluid, so water moves out of the cells to balance that (fig. 24.5). Ultimately, all three fluid compartments (the intracellular fluid, blood, and tissue fluid) lose water. To excrete 1 L of sweat, about 300 mL of water would come from the ECF and 700 mL from the ICF.
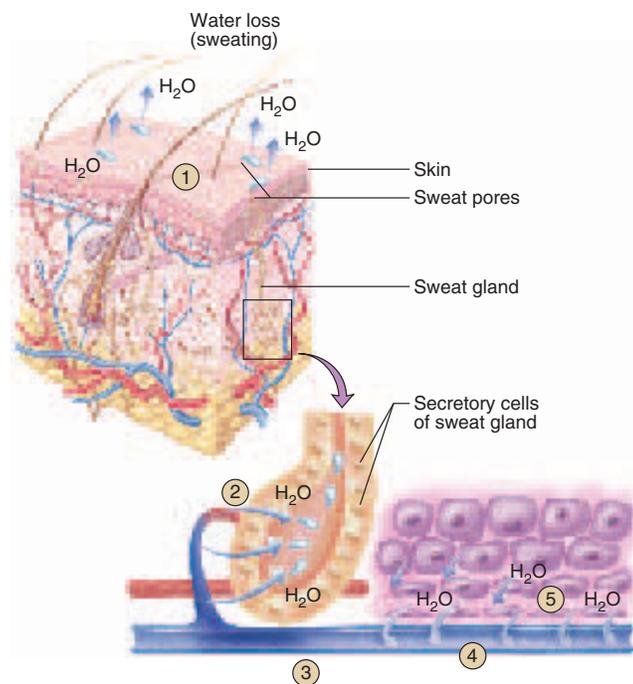

Figure 24.5   Effects of Profuse Sweating on the Fluid Compartments. (*1*) Sweat is released from pores in the skin. (*2*) Sweat is produced by filtration from the blood capillaries. (*3*) As fluid is taken from the bloodstream, blood volume and pressure drop and blood osmolarity rises. (*4*) The blood absorbs tissue fluid to replace its loss. (*5*) Fluid is transferred from the intracellular compartment to the tissue fluid. In severe dehydration, this results in cell shrinkage and malfunction.

Immoderate exercise without fluid replacement can lead to even greater loss than 1 L per hour.

The most serious effects of fluid deficiency are circulatory shock due to loss of blood volume and neurological dysfunction due to dehydration of brain cells. Volume depletion by diarrhea is a major cause of infant mortality, especially under unsanitary conditions that lead to intestinal infections such as cholera.

Insight 24.1   Clinical Application

Fluid Balance in Cold Weather

Hot weather and profuse sweating are obvious threats to fluid balance, but so is cold weather. The body conserves heat by constricting the blood vessels of the skin and subcutaneous tissue, thus forcing blood into the deeper circulation. This raises the blood pressure, which inhibits the secretion of antidiuretic hormone and increases the secretion of atrial natriuretic peptide. These hormones increase urine output and reduce blood volume. In addition, cold air is relatively dry and increases respiratory water loss. This is why exercise causes the respiratory tract to "burn" more in cold weather than in warm.

These cold-weather respiratory and urinary losses can cause significant hypovolemia. Furthermore, the onset of exercise stimulates vasodilation in the skeletal muscles. In a hypovolemic state, there may not be enough blood to supply them and a person may experience weakness, fatigue, or fainting (hypovolemic shock). In winter sports and other activities such as snow shoveling, it is important to maintain fluid balance. Even if you do not feel thirsty, it is beneficial to take ample amounts of warm liquids such as soup or cider. Coffee, tea, and alcohol, however, have diuretic effects that defeat the purpose of fluid intake.

Fluid Excess

Fluid excess is less common than fluid deficiency because the kidneys are highly effective at compensating for excessive intake by excreting more urine (fig. 24.6). Renal failure and other causes, however, can lead to excess fluid retention.

Fluid excesses are of two types called volume excess and hypotonic hydration. In **volume excess,** both sodium and water are retained and the ECF remains isotonic. Volume excess can result from aldosterone hypersecretion or renal failure. In **hypotonic hydration** (also called **water intoxication** or **positive water balance**), more water than sodium is retained or ingested and the ECF becomes hypotonic. This can occur if you lose a large amount of water *and* salt through urine and sweat and you replace it by drinking plain water. Without a proportionate intake of electrolytes, water dilutes the ECF, makes it hypotonic, and causes cellular swelling. ADH hypersecretion can cause hypotonic hydration by stimulating excessive water retention as sodium continues to be excreted. Among the most serious effects of either type of fluid excess are pulmonary and cerebral edema.
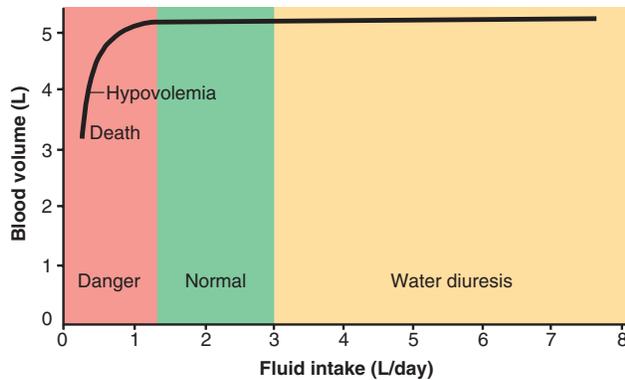
Figure 24.6 **The Relationship of Blood Volume to Fluid Intake.** The kidneys cannot compensate very well for inadequate fluid intake. Below an intake of about 1 L/day, blood volume drops significantly and there may be a threat of death from hypovolemic shock. The kidneys compensate very well, on the other hand, for abnormally high fluid intake; they eliminate the excess by water diuresis and maintain a stable blood volume.

Fluid Sequestration

Fluid sequestration[3] (seh-ques-TRAY-shun) is a condition in which excess fluid accumulates in a particular location. Total body water may be normal, but the volume of circulating blood may drop to the point of causing circulatory shock. The most common form of sequestration is *edema,* the abnormal accumulation of fluid in the interstitial spaces, causing swelling of a tissue (discussed in detail in chapter 20). Hemorrhage can be another cause of fluid sequestration; blood that pools and clots in the tissues is lost to circulation. Yet another example is *pleural effusion,* caused by some lung infections, in which several liters of fluid accumulate in the pleural cavity.

The four principal forms of fluid imbalance are summarized and compared in table 24.1.

Think About It

Some tumors of the brain, pancreas, and small intestine secrete ADH. What type of water imbalance would this produce? Explain why.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

1. List five routes of water loss. Which one accounts for the greatest loss? Which one is most controllable?
2. Explain why even a severely dehydrated person inevitably experiences further fluid loss.

[3]*sequestr* = to isolate

Table 24.1	Forms of Fluid Imbalance	
	Total Body Water	**Osmolarity**
Fluid Deficiency		
Volume depletion (hypovolemia)	Reduced	Isotonic (normal)
Dehydration (negative water balance)	Reduced	Hypertonic (elevated)
Fluid Excess		
Volume excess	Elevated	Isotonic (normal)
Hypotonic hydration (positive water balance, water intoxication)	Elevated	Hypotonic (reduced)

3. Suppose there were no mechanisms to stop the sense of thirst until the blood became sufficiently hydrated. Explain why we would routinely suffer hypotonic hydration.
4. Summarize the effect of ADH on total body water and blood osmolarity.
5. Name and define the four types of fluid imbalance, and give an example of a situation that could produce each type.

Electrolyte Balance

Objectives

When you have completed this section, you should be able to
- describe the physiological roles of sodium, potassium, calcium, chloride, and phosphate;
- describe the hormonal and renal mechanisms that regulate the concentrations of these electrolytes; and
- state the term for an excess or deficiency of each electrolyte and describe the consequences of these imbalances.

Electrolytes are physiologically important for multiple reasons: They are chemically reactive and participate in metabolism, they determine the electrical potential (charge difference) across cell membranes, and they strongly affect the osmolarity of the body fluids and the body's water content and distribution. Strictly speaking, electrolytes are salts such as sodium chloride, not just sodium or chloride ions. In common usage, however, the individual ions are often referred to as electrolytes. The major cations are sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and hydrogen (H^+), and the major anions are chloride (Cl^-), bicarbonate (HCO_3^-), and phosphates (P_i). Hydrogen and bicarbonate regulation are discussed later under acid-base balance. Here we focus on the other five.

The typical concentrations of these ions and the terms for electrolyte imbalances are listed in table 24.2. Blood plasma is the most accessible fluid for measurements of electrolyte concentration, so excesses and deficiencies are defined with reference to normal plasma concentrations. Concentrations in the tissue fluid differ only slightly from those in the plasma. The prefix *normo-* denotes a normal electrolyte concentration (for example, *normokalemia*), and *hyper-* and *hypo-* denote concentrations that are sufficiently above or below normal to cause physiological disorders.

Sodium

Functions

Sodium is one of the principal ions responsible for the resting membrane potentials of cells, and the inflow of sodium through gated membrane channels is an essential event in the depolarization that underlies nerve and muscle function. Sodium is the principal cation of the ECF; sodium salts account for 90% to 95% of its osmolarity. Sodium is therefore the most significant solute in determining total body water and the distribution of water among fluid compartments. Sodium gradients across the plasma membrane provide the potential energy that is tapped to cotransport other solutes such as glucose, potassium, and calcium. The Na^+-K^+ pump is an important mechanism for generating body heat. Sodium bicarbonate ($NaHCO_3$) plays a major role in buffering the pH of the ECF.

Homeostasis

An adult needs about 0.5 g of sodium per day, whereas the typical American diet contains 3 to 7 g/day. Thus a dietary sodium deficiency is rare, and the primary concern is adequate excretion of the excess. This is one of the most important roles of the kidneys. There are multiple mechanisms for controlling sodium concentration, tied to its effects on blood pressure and osmolarity and coordinated by three hormones: aldosterone, antidiuretic hormone, and atrial natriuretic peptide.

Aldosterone, the "salt-retaining hormone," plays the primary role in adjustment of sodium excretion. Hyponatremia and hyperkalemia directly stimulate the adrenal cortex to secrete aldosterone, and hypotension stimulates its secretion by way of the renin-angiotensin mechanism (fig. 24.7).

Only cells of the distal convoluted tubule and cortical part of the collecting duct have aldosterone receptors. Aldosterone, a steroid, binds to nuclear receptors and activates transcription of a gene for the Na^+-K^+ pump. In 10 to 30 minutes, enough Na^+-K^+ pumps are synthesized and installed in the plasma membrane to produce a noticeable effect—sodium concentration in the urine begins to fall and potassium concentration rises as the tubules reabsorb more Na^+ and secrete more H^+ and K^+. Water and Cl^- passively follow Na^+. Thus the primary effects of aldosterone are that the urine contains less NaCl and more K^+ and has a lower pH. An average adult male excretes 5 g of sodium per day, but the urine can be virtually sodium-free when aldosterone level is high. Although aldosterone strongly influences sodium reabsorption, it has little effect on plasma sodium *concentration* because reabsorbed sodium is accompanied by a proportionate amount of water.

Hypertension inhibits the renin-angiotensin-aldosterone mechanism. The kidneys then reabsorb almost no sodium beyond the proximal convoluted tubule (PCT), and the urine contains up to 30 g of sodium per day.

Aldosterone has only slight effects on urine volume, blood volume, and blood pressure in spite of the tendency of water to follow sodium osmotically. Even in aldosterone hypersecretion, blood volume is rarely more than 5% to 10% above normal. An increase in blood volume increases blood pressure and glomerular filtration rate (GFR). Even though aldosterone increases the tubular reabsorption of

Table 24.2   Electrolyte Concentrations and the Terminology of Electrolyte Imbalances

Electrolyte	Mean Concentration (mEq/L)*		Deficiency	Excess
	Plasma	**ICF**		
Sodium (Na^+)	142	10	Hyponatremia	Hypernatremia[4]
Potassium (K^+)	5	141	Hypokalemia	Hyperkalemia[5]
Calcium (Ca^{2+})	5	<1	Hypocalcemia	Hypercalcemia
Chloride (Cl^-)	103	4	Hypochloremia	Hyperchloremia
Phosphate (PO_4^{3-})	4	75	Hypophosphatemia	Hyperphosphatemia

*Concentrations in mmol/L are the same for Na^+, K^+, and Cl^-, one-half the above values for Ca^{2+}, and one-third the above values for PO_4^{3-}.
[4]*natr* = sodium + *emia* = blood condition
[5]*kal* = potassium

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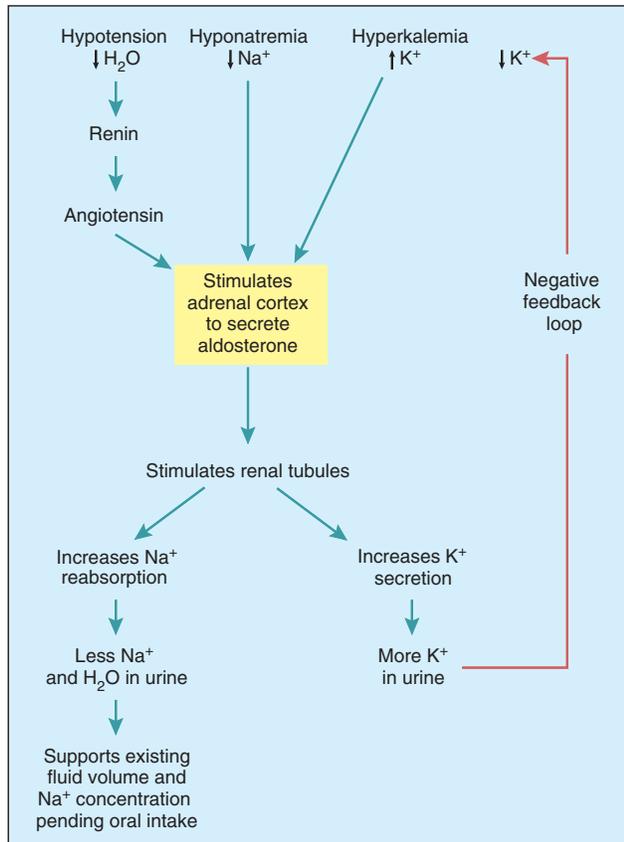Acid–Base Balance

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Figure 24.7 **The Secretion and Effects of Aldosterone.** The pathway shown in *red* represents negative feedback.
What is required, in addition to aldosterone, to increase blood volume?

Several other hormones also affect sodium homeostasis. Estrogens mimic the effect of aldosterone and cause women to retain water during pregnancy and part of the menstrual cycle. Progesterone reduces sodium reabsorption and has a diuretic effect. High levels of glucocorticoids promote sodium reabsorption and edema.

In some cases, sodium homeostasis is achieved by regulation of salt intake. A craving for salt occurs in people who are depleted of sodium; for example, by blood loss or Addison disease. Pregnant women sometimes develop a craving for salty foods. Salt craving is not limited to humans; many animals ranging from elephants to butterflies seek out salty soil where they can obtain this vital mineral.

Imbalances

True imbalances in sodium concentration are relatively rare because sodium excess or depletion is almost always accompanied by proportionate changes in water volume. **Hypernatremia** is a plasma sodium concentration in excess of 145 mEq/L. It can result from the administration of intravenous saline (see insight 24.2, p. 933). Its major consequences are water retention, hypertension, and edema. **Hyponatremia** (less than 130 mEq/L) is usually the result of excess body water rather than excess sodium excretion, as in the case mentioned earlier of a person who loses large volumes of sweat or urine and replaces it by drinking plain water. Usually, hyponatremia is quickly corrected by excretion of the excess water, but if uncorrected it produces the symptoms of hypotonic hydration described earlier.

Potassium

Functions

Potassium is the most abundant cation of the ICF and is the greatest determinant of intracellular osmolarity and cell volume. Along with sodium, it produces the resting membrane potentials and action potentials of nerve and muscle cells (fig. 24.8*a*). Potassium is as important as sodium to the Na^+-K^+ pump and its functions of cotransport and thermogenesis (heat production). It is an essential cofactor for protein synthesis and some other metabolic processes.

Homeostasis

Potassium homeostasis is closely linked to that of sodium. Regardless of the body's state of potassium balance, about 90% of the K^+ filtered by the glomerulus is reabsorbed by the PCT and the rest is excreted in the urine. Variations in potassium excretion are controlled later in the nephron by changing the amount of potassium returned to the tubular fluid by the distal convoluted tubule and cortical portion

sodium and water, this is offset by the rise in GFR and there is only a small drop in urine output.

Antidiuretic hormone modifies water excretion independently of sodium excretion. Thus, unlike aldosterone, it can change sodium *concentration.* A high concentration of sodium in the blood stimulates the posterior lobe of the pituitary gland to release ADH. Thus the kidneys reabsorb more water, which slows down any further increase in blood sodium concentration. ADH alone cannot lower the blood sodium concentration; this requires water ingestion, but remember that ADH also stimulates thirst. A drop in sodium concentration, by contrast, inhibits ADH release. More water is excreted and this raises the concentration of the sodium that remains in the blood.

Atrial natriuretic peptide (ANP) inhibits sodium and water reabsorption and the secretion of renin and ADH. The kidneys thus eliminate more sodium and water and lower the blood pressure.
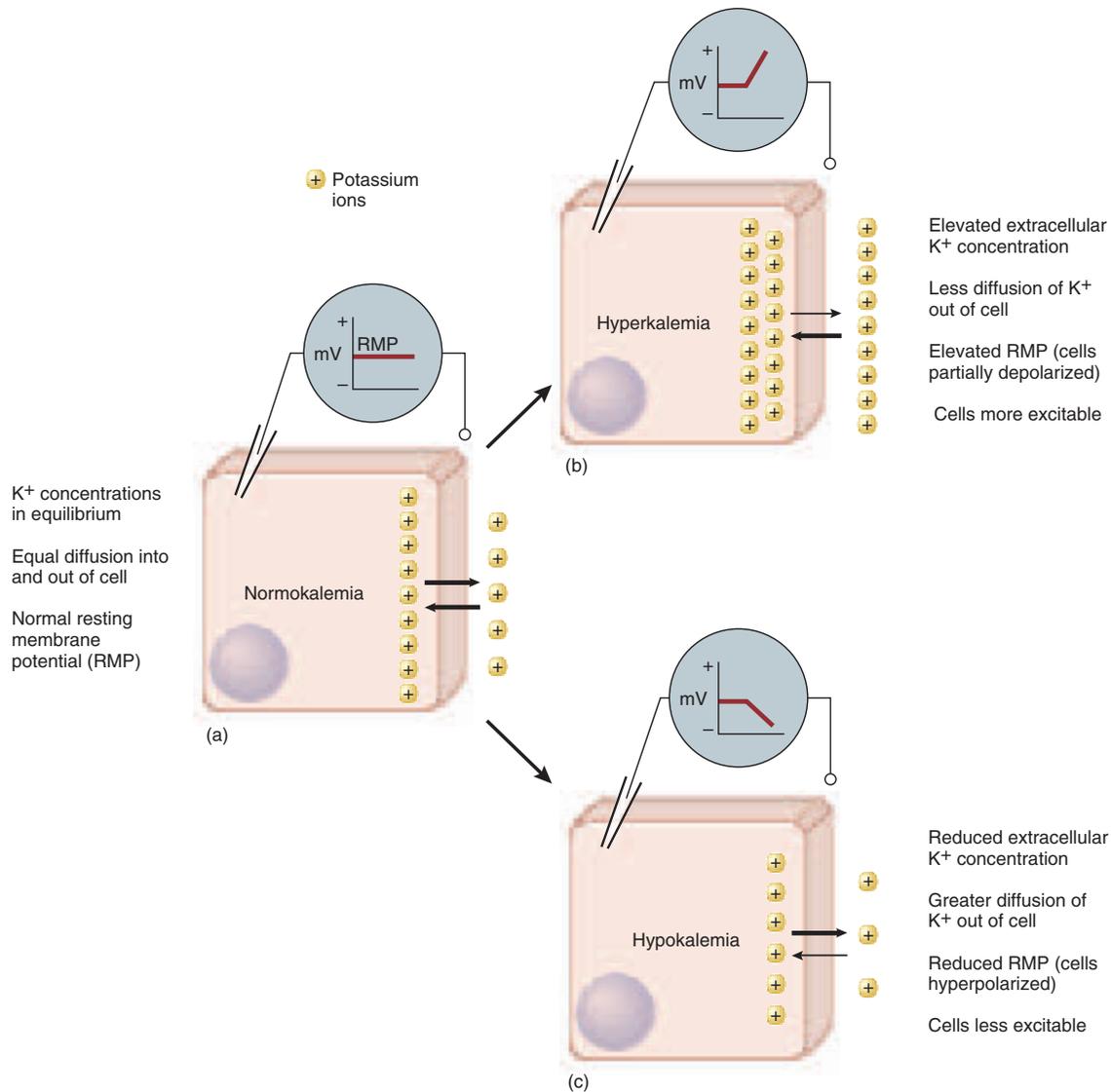
Figure 24.8 Effects of Potassium Imbalances on Membrane Potentials. The circular diagram above each cell represents the voltage measured across the plasma membrane. (*a*) Normokalemia, with a normal resting membrane potential (RMP). (*b*) Hyperkalemia, with an elevated RMP. (*c*) Hypokalemia, with a depressed RMP.

of the collecting duct (CD). When K^+ concentration is high, they secrete more K^+ into the filtrate and the urine may contain more K^+ than the glomerulus filters from the blood. When blood K^+ level is low, the CD secretes less. The intercalated cells of the distal convoluted tubule and collecting duct reabsorb K^+.

Aldosterone regulates potassium balance along with sodium (see fig. 24.7). A rise in K^+ concentration stimulates the adrenal cortex to secrete aldosterone. Aldosterone stimulates renal secretion of K^+ at the same time that it

stimulates reabsorption of sodium. The more sodium there is in the urine, the less potassium, and vice versa.

Imbalances

Potassium imbalances are the most dangerous of all electrolyte imbalances. **Hyperkalemia** (> 5.5 mEq/L) can have completely opposite effects depending on whether K^+ concentration rises quickly or slowly. It can rise quickly when, for example, a crush injury or hemolytic anemia

releases large amounts of K^+ from ruptured cells. This can also result from a transfusion with outdated, stored blood because K^+ leaks from erythrocytes into the plasma during storage. A sudden increase in extracellular K^+ tends to make nerve and muscle cells abnormally excitable. Normally, K^+ continually passes in and out of cells at equal rates—leaving by diffusion and reentering by the Na^+-K^+ pump. But in hyperkalemia, there is less concentration difference between the ICF and ECF, so the outward diffusion of K^+ is reduced. More K^+ remains in the cell than normal, and the plasma membrane therefore has a less negative resting potential and is closer to the threshold at which it will set off action potentials (fig. 24.8b). This is a very dangerous condition that can quickly produce cardiac arrest. High-potassium solutions are sometimes used by veterinarians to euthanize animals and are used in some states as a lethal injection for capital punishment.

Hyperkalemia can also have a slower onset stemming from such causes as aldosterone hyposecretion, renal failure, or acidosis. (The relationship of acid-base imbalances to potassium imbalances is explained later.) Paradoxically, if the extracellular K^+ concentration rises slowly, nerve and muscle become *less* excitable. *Slow* depolarization of a cell inactivates voltage-gated Na^+ channels, and the channels do not become excitable again until the membrane repolarizes. Inactivated Na^+ channels cannot produce action potentials. For this reason, muscle cramps can be relieved by taking supplemental potassium.

Hypokalemia (<3.5 mEq/L) rarely results from a dietary deficiency, because most diets contain ample amounts of potassium; it can occur, however, in people with depressed appetites. Hypokalemia more often results from heavy sweating, chronic vomiting or diarrhea, excessive use of laxatives, aldosterone hypersecretion, or alkalosis. As ECF potassium concentration falls, more K^+ moves from the ICF to the ECF. With the loss of these cations from the cytoplasm, cells become hyperpolarized and nerve and muscle cells are less excitable (fig. 24.8c). This is reflected in muscle weakness, loss of muscle tone, depressed reflexes, and irregular electrical activity of the heart.

Think About It

Some tumors of the adrenal cortex secrete excess aldosterone and may cause paralysis. Explain this effect and identify the electrolyte and fluid imbalances you would expect to observe in such a case.

Chloride

Functions

Chloride ions are the most abundant anions of the ECF and thus make a major contribution to its osmolarity. Chloride ions are required for the formation of stomach acid (HCl), and they are involved in the chloride shift that accompanies carbon dioxide loading and unloading by the erythrocytes (see chapter 22). By a similar mechanism explained later, Cl^- plays a major role in the regulation of body pH.

Homeostasis

Cl^- is strongly attracted to Na^+, K^+, and Ca^{2+}. It would require great expenditure of energy to keep it separate from these cations, so Cl^- homeostasis is achieved primarily as an effect of Na^+ homeostasis—as sodium is retained or excreted, Cl^- passively follows.

Imbalances

Hyperchloremia (>105 mEq/L) is usually the result of dietary excess or administration of intravenous saline. **Hypochloremia** (<95 mEq/L) is usually a side effect of hyponatremia but sometimes results from hypokalemia. In the latter case, the kidneys retain K^+ by excreting more Na^+, and Na^+ takes Cl^- with it. The primary effects of chloride imbalances are disturbances in acid-base balance, but this works both ways—a pH imbalance arising from some other cause can also produce a chloride imbalance. Chloride balance is therefore discussed further in connection with acid-base balance.

Calcium

Functions

Calcium lends strength to the skeleton, activates the sliding filament mechanism of muscle contraction, serves as a second messenger for some hormones and neurotransmitters, activates exocytosis of neurotransmitters and other cellular secretions, and is an essential factor in blood clotting. Cells maintain a very low intracellular calcium concentration because they require a high concentration of phosphate ions (for reasons discussed shortly). If calcium and phosphate were both very concentrated in a cell, calcium phosphate crystals would precipitate in the cytoplasm (as described in chapter 7). To maintain a high phosphate concentration but avoid crystallization of calcium phosphate, cells must pump out Ca^{2+} and keep it at a low intracellular concentration or else sequester Ca^{2+} in the smooth ER and release it only when needed. Cells that store Ca^{2+} often have a protein called *calsequestrin,* which binds the stored Ca^{2+} and keeps it chemically unreactive.

Homeostasis

The homeostatic control of Ca^{2+} concentration was discussed extensively in chapter 7. It is regulated chiefly by

parathyroid hormone, calcitriol, and in children, by calcitonin. These hormones regulate blood calcium concentration through their effects on bone deposition and resorption, intestinal absorption of calcium, and urinary excretion.

Imbalances

Hypercalcemia (>5.8 mEq/L) can result from alkalosis, hyperparathyroidism, or hypothyroidism. It reduces the Na^+ permeability of plasma membranes and inhibits the depolarization of nerve and muscle cells. At concentrations $\geq$ 12 mEq/dL, hypercalcemia causes muscular weakness, depressed reflexes, and cardiac arrhythmia.

Hypocalcemia (<4.5 mEq/L) can result from vitamin D deficiency, diarrhea, pregnancy, lactation, acidosis, hypoparathyroidism, or hyperthyroidism. It increases the Na^+ permeability of plasma membranes causing the nervous and muscular systems to be overly excitable. Tetany occurs when calcium concentration drops to 6 mg/dL and may be lethal at 4 mg/dL due to laryngospasm and suffocation.

Phosphates

Functions

The inorganic phosphates (P_i) of the body fluids are an equilibrium mixture of phosphate (PO_4^{3-}), monohydrogen phosphate (HPO_4^{2-}), and dihydrogen phosphate ($H_2PO_4^{-}$) ions. Phosphates are relatively concentrated in the ICF, where they are generated by the hydrolysis of ATP and other phosphate compounds. They are a component of nucleic acids, phospholipids, ATP, GTP, cAMP, and related compounds. Every process that depends on ATP depends on phosphate ions. Phosphates activate many metabolic pathways by phosphorylating enzymes and substrates such as glucose. They are also important as buffers that help stabilize the pH of the body fluids.

Homeostasis

The average diet provides ample amounts of phosphate ions, which are readily absorbed by the small intestine. Plasma phosphate concentration is usually maintained at about 4 mEq/L, with continual loss of excess phosphate by glomerular filtration. If plasma phosphate concentration drops much below this level, however, the renal tubules reabsorb all filtered phosphate.

Parathyroid hormone increases the excretion of phosphate as part of the mechanism for increasing the concentration of free calcium ions in the ECF. Lowering the ECF phosphate concentration minimizes the formation of calcium phosphate and thus helps support plasma calcium concentration. Rates of phosphate excretion are also strongly affected by the pH of the urine, as discussed shortly.

Imbalances

Phosphate homeostasis is not as critical as that of other electrolytes. The body can tolerate broad variations several times above or below the normal concentration with little immediate effect on physiology.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

6. Which of these do you think would have the most serious effect, and why—a 5 mEq/L increase in the plasma concentration of sodium, potassium, chloride, or calcium?
7. Answer the same question for a 5 mEq/L *decrease.*
8. Explain why ADH is more likely than aldosterone to change the osmolarity of the blood plasma.
9. Explain why aldosterone hyposecretion could cause hypochloremia.
10. Why are more phosphate ions required in the ICF than in the ECF? How does this affect the distribution of calcium ions between these fluid compartments?

Acid-Base Balance

Objectives

When you have completed this section, you should be able to
- define *buffer* and write chemical equations for the bicarbonate, phosphate, and protein buffer systems;
- discuss the relationship between pulmonary ventilation, pH of the extracellular fluids, and the bicarbonate buffer system;
- explain how the kidneys secrete hydrogen ions and how these ions are buffered in the tubular fluid;
- identify some types and causes of acidosis and alkalosis, and describe the effects of these pH imbalances; and
- explain how the respiratory and urinary systems correct acidosis and alkalosis, and compare their effectiveness and limitations.

As we saw in chapter 2, metabolism depends on the functioning of enzymes, and enzymes are very sensitive to pH. Slight deviations from the normal pH can shut down metabolic pathways as well as alter the structure and function of other macromolecules. Consequently, acid-base balance is one of the most important aspects of homeostasis.

The blood and tissue fluid normally have a pH of 7.35 to 7.45. Such a narrow range of variation is remarkable considering that our metabolism constantly produces acid: lactic acid from anaerobic fermentation, phosphoric acids from nucleic acid catabolism, fatty acids and ketones from fat catabolism, and carbonic acid from carbon dioxide. Here we examine mechanisms for resisting these challenges and maintaining acid-base balance.

Think About It

In the systemic circulation, arterial blood has a pH of 7.40 and venous blood has a pH of 7.35. What do you think causes this difference?

Acids, Bases, and Buffers

The pH of a solution is determined solely by its hydrogen ions (H^+) (or strictly speaking, hydronium ions, H_3O^+, as explained in chapter 2). An acid is any chemical that releases H^+ in solution. A **strong acid** such as hydrochloric acid (HCl) ionizes freely, gives up most of its hydrogen ions, and can markedly lower the pH of a solution. A **weak acid** such as carbonic acid (H_2CO_3) ionizes only slightly and keeps most hydrogen in a chemically bound form that does not affect pH. A base is any chemical that accepts H^+. A **strong base** such as the hydroxyl ion (OH^-) has a strong tendency to bind H^+ and raise the pH, whereas a **weak base** such as the bicarbonate ion (HCO_3^-) binds less of the available H^+ and has less effect on pH.

A **buffer,** broadly speaking, is any mechanism that resists changes in pH by converting a strong acid or base to a weak one. The body has both physiological and chemical buffers. A **physiological buffer** is a system—namely the respiratory or urinary system—that stabilizes pH by controlling the body's output of acids, bases, or CO_2. Of all buffer systems, the urinary system buffers the greatest quantity of acid or base, but it requires several hours to days to exert an effect. The respiratory system exerts an effect within a few minutes but cannot alter the pH as much as the urinary system can.

A **chemical buffer** is a substance that binds H^+ and removes it from solution as its concentration begins to rise or releases H^+ into solution as its concentration falls. Chemical buffers can restore normal pH within a fraction of a second. They function as mixtures called **buffer systems** composed of a weak acid and a weak base. The three major chemical buffer systems of the body are the bicarbonate, phosphate, and protein systems.

The amount of acid or base that can be neutralized by a chemical buffer system depends on two factors: the concentration of the buffers and the pH of their working environment. Each system has an optimum pH at which it functions best; its effectiveness is greatly reduced if the pH of its environment deviates too far from this. The relevance of these factors will become apparent as you study the following buffer systems.

The Bicarbonate Buffer System

The **bicarbonate buffer system** is a solution of carbonic acid and bicarbonate ions. Carbonic acid (H_2CO_3) forms by the hydration of carbon dioxide and then dissociates into bicarbonate (HCO_3^-) and H^+:

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

This is a reversible reaction. When it proceeds to the right, carbonic acid acts as a weak acid by releasing H^+ and lowering pH. When the reaction proceeds to the left, bicarbonate acts as a weak base by binding H^+, removing the ions from solution, and raising pH.

At a pH of 7.4, the bicarbonate system would not ordinarily have a particularly strong buffering capacity outside of the body. This is too far from its optimum pH of 6.1. If a strong acid were added to a beaker of carbonic acid–bicarbonate solution at pH 7.4, the preceding reaction would shift only slightly to the left. Much surplus H^+ would remain and the pH would be substantially lower. In the body, by contrast, the bicarbonate system works quite well because the lungs and kidneys constantly remove CO_2 and prevent an equilibrium from being reached. This keeps the reaction moving to the left, and more H^+ is neutralized. Conversely, if there is a need to lower the pH, the kidneys excrete HCO_3^-, keep this reaction moving to the right, and elevate the H^+ concentration of the ECF. Thus you can see that the physiological and chemical buffers of the body function together in maintaining acid-base balance.

The Phosphate Buffer System

The **phosphate buffer system** is a solution of HPO_4^{2-} and $H_2PO_4^-$. It works in much the same way as the bicarbonate system. The following reaction can proceed to the right to liberate H^+ and lower pH, or it can proceed to the left to bind H^+ and raise pH:

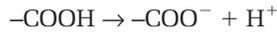$$H_2PO_4^- \leftrightarrow HPO_4^{2-} + H^+$$

The optimal pH for this system is 6.8, closer to the actual pH of the ECF. Thus the phosphate buffer system has a stronger buffering effect than an equal amount of bicarbonate buffer. However, phosphates are much less concentrated in the ECF than bicarbonate, so they are less important in buffering the ECF. They are more important in the renal tubules and ICF, where not only are they more concentrated, but the pH is lower and closer to their functional optimum. In the ICF, the constant production of metabolic acids creates pH values ranging from 4.5 to 7.4, probably averaging 7.0. The reason for the low pH in the renal tubules is discussed later.
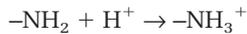
The Protein Buffer System

Proteins are more concentrated than either bicarbonate or phosphate buffers, especially in the ICF. The **protein buffer system** accounts for about three-quarters of all chemical buffering ability of the body fluids. The buffering ability of proteins is due to certain side groups of their amino acid residues. Some have carboxyl (–COOH) side

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24. Water, Electrolyte, and
Acid–Base Balance

Text

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groups, which release H^+ when pH begins to rise and thus lower pH:

$$-COOH \rightarrow -COO^- + H^+$$

Others have amino ($-NH_2$) side groups, which bind H^+ when pH falls too low, thus raising pH toward normal:

$$-NH_2 + H^+ \rightarrow -NH_3{}^+$$

Think About It

What protein do you think is the most important buffer in blood plasma? In erythrocytes?

Respiratory Control of pH

The equation for the bicarbonate buffer system shows that the addition of CO_2 to the body fluids raises H^+ concentration and lowers pH, while the removal of CO_2 has the opposite effects. This is the basis for the strong buffering capacity of the respiratory system. Indeed, this system can neutralize two or three times as much acid as the chemical buffers can.

Carbon dioxide is constantly produced by aerobic metabolism and is normally eliminated by the lungs at an equivalent rate. As explained in chapter 22, rising CO_2 concentration and falling pH stimulate peripheral and central chemoreceptors, which stimulate an increase in pulmonary ventilation. This expels excess CO_2 and thus reduces H^+ concentration. The free H^+ becomes part of the water molecules produced by this reaction:

$$HCO_3{}^- + H^+ \rightarrow H_2CO_3 \rightarrow CO_2 \text{ (expired)} + H_2O$$
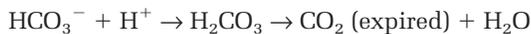
Conversely, a drop in H^+ concentration raises pH and reduces pulmonary ventilation. This allows metabolic CO_2 to accumulate in the ECF faster than it is expelled, thus lowering pH to normal.

These are classic negative feedback mechanisms that result in acid-base homeostasis. Respiratory control of pH has some limitations, however, which are discussed later under acid-base imbalances.

Renal Control of pH

The kidneys can neutralize more acid or base than either the respiratory system or the chemical buffers. The essence of this mechanism is that the renal tubules secrete H^+ into the tubular fluid, where most of it binds to bicarbonate, ammonia, and phosphate buffers. Bound and free H^+ are then excreted in the urine. Thus the kidneys, in contrast to the lungs, actually expel H^+ from the body. The other buffer systems only reduce its concentration by binding it to another chemical.

Figure 24.9 shows the process of H^+ secretion and neutralization. It is numbered to correspond to the following description, and the hydrogen ions are shown in color

so you can trace them through the system from blood to urine:

1. Hydrogen ions in the blood are neutralized in two ways: by reacting with bicarbonate ions to produce carbonic acid and with hydroxyl ions to produce water.
2. Carbonic acid dissociates into water and carbon dioxide, which diffuse into the tubule cells.
3. The tubule cells obtain CO_2 from three sources: the blood, the tubular fluid, and their own aerobic respiration.
4. Within the tubule cell, carbonic anhydrase (CAH) catalyzes the reaction of CO_2 and H_2O to produce carbonic acid.
5. Carbonic acid dissociates into bicarbonate and hydrogen ions.
6. The bicarbonate ions diffuse back into the bloodstream and may reenter the reaction cycle.
7. An antiport in the tubule cells pumps H^+ into the tubular fluid in exchange for Na^+.
8. Sodium bicarbonate ($NaHCO_3$) in the glomerular filtrate reacts with these hydrogen ions producing free sodium ions and carbonic acid.
9. The sodium ions are pumped into the tubule cells by the antiport at step 7 and then transferred to the blood by a Na^+-K^+ pump in the basal plasma membrane.
10. The carbonic acid in the tubular fluid dissociates into carbon dioxide and water. (The role of CAH is discussed shortly.) The CO_2 is recycled into the tubule cell and the water may be passed in the urine. Thus the hydrogen ions removed from the blood at step 1 are now part of the water molecules excreted in the urine at step 10.

Tubular secretion of H^+ (step 7) continues only as long as there is a sufficient concentration gradient between a high H^+ concentration in the tubule cells and a lower H^+ concentration in the tubular fluid. If the pH of the tubular fluid drops any lower than 4.5, tubular secretion of H^+ (step 7) ceases for lack of a sufficient gradient. Thus, pH 4.5 is the **limiting pH** for tubular secretion of H^+. This has added significance later in our discussion.

In a person with normal acid-base balance, the tubules secrete enough H^+ to neutralize all $HCO_3{}^-$ in the tubular fluid; thus there is no $HCO_3{}^-$ in the urine. Bicarbonate ions are filtered by the glomerulus, gradually disappear from the tubular fluid, and appear in the peritubular capillary blood. It *appears* as if $HCO_3{}^-$ were reabsorbed by the renal tubules, but this is not the case; indeed, the renal tubules are incapable of $HCO_3{}^-$ reabsorption. The cells of the proximal convoluted tubule, however, have carbonic anhydrase (CAH) on their brush borders facing the lumen. This breaks down the H_2CO_3 in the tubular fluid to $CO_2 + H_2O$ (step 10). It is the CO_2 that
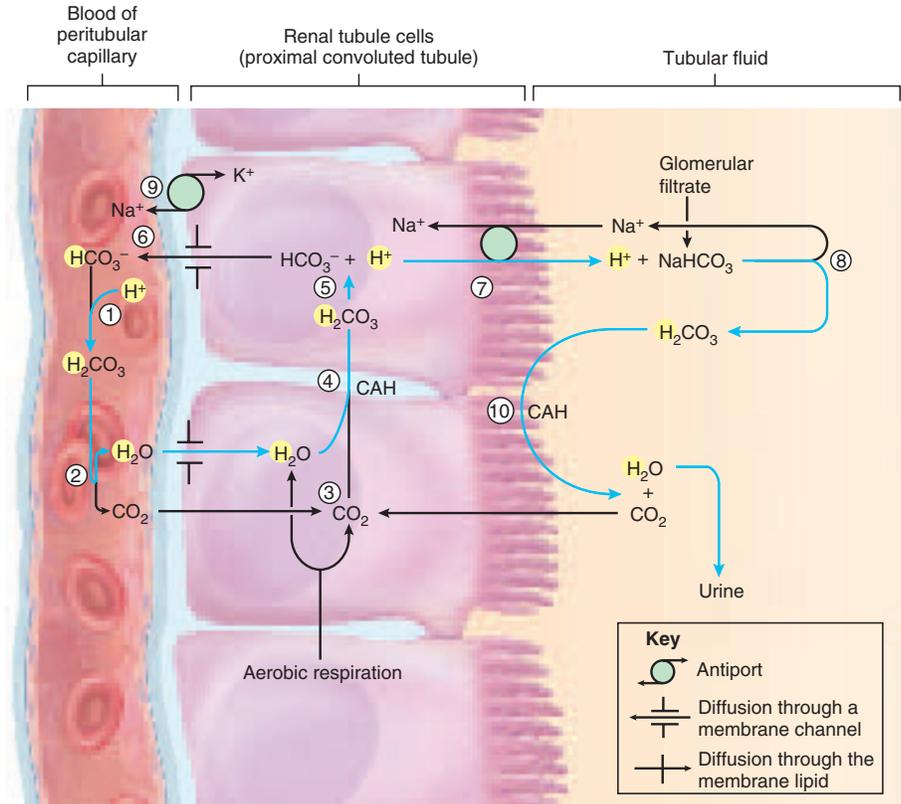
Figure 24.9 **Secretion and Neutralization of Hydrogen Ions in the Kidneys.** Circled numbers correspond to the explanation in the text. The colored arrows and hydrogen symbols allow you to trace hydrogen from H^+ in the blood to H_2O in the urine.
If the pH of the tubular fluid went down, how would its Na^+ concentration change?

is reabsorbed, not the bicarbonate. For every CO_2 reabsorbed, however, a *new* bicarbonate ion is formed in the tubule cell and released into the blood (steps 5–6). The effect is the same as if the tubule cells had reabsorbed bicarbonate itself.

Note that for every bicarbonate ion that enters the peritubular capillaries, a sodium ion does too. Thus the reabsorption of Na^+ by the renal tubules is part of the process of neutralizing acid. The more acid the kidneys excrete, the less sodium the urine contains.

The tubules secrete somewhat more H^+ than the available bicarbonate can neutralize. The urine therefore contains a slight excess of free H^+, which gives it a pH of about 5 to 6. Yet if all of the excess H^+ secreted by the tubules remained in this free ionic form, the pH of the tubular fluid would drop far below the limiting pH of 4.5, and H^+ secretion would stop. This must be prevented, and there are additional buffers in the tubular fluid to do so.

The glomerular filtrate contains Na_2HPO_4 (dibasic sodium phosphate), which reacts with some of the H^+

(fig. 24.10). A hydrogen ion replaces one of the sodium ions in the buffer, forming NaH_2PO_4 (monobasic sodium phosphate). This is passed in the urine and the displaced Na^+ is transported into the tubule cell and from there to the bloodstream.

In addition, tubular cells catabolize certain amino acids and release ammonia (NH_3) as a product (fig. 24.10). Ammonia diffuses into the tubular fluid, where it acts as a base to neutralize acid. It reacts with H^+ and Cl^- (the most abundant anion in the glomerular filtrate) to form ammonium chloride (NH_4Cl), which is passed in the urine.

Since there is so much chloride in the tubular fluid, you might ask why H^+ is not simply excreted as hydrochloric acid (HCl). Why involve ammonia? The reason is that HCl is a strong acid—it dissociates almost completely, so most of its hydrogen would be in the form of free H^+. The pH of the tubular fluid would drop below the limiting pH and prevent excretion of more acid. Ammonium chloride, by contrast, is a weak acid—most of its hydrogen remains bound to it and does not lower the pH of the tubular fluid.

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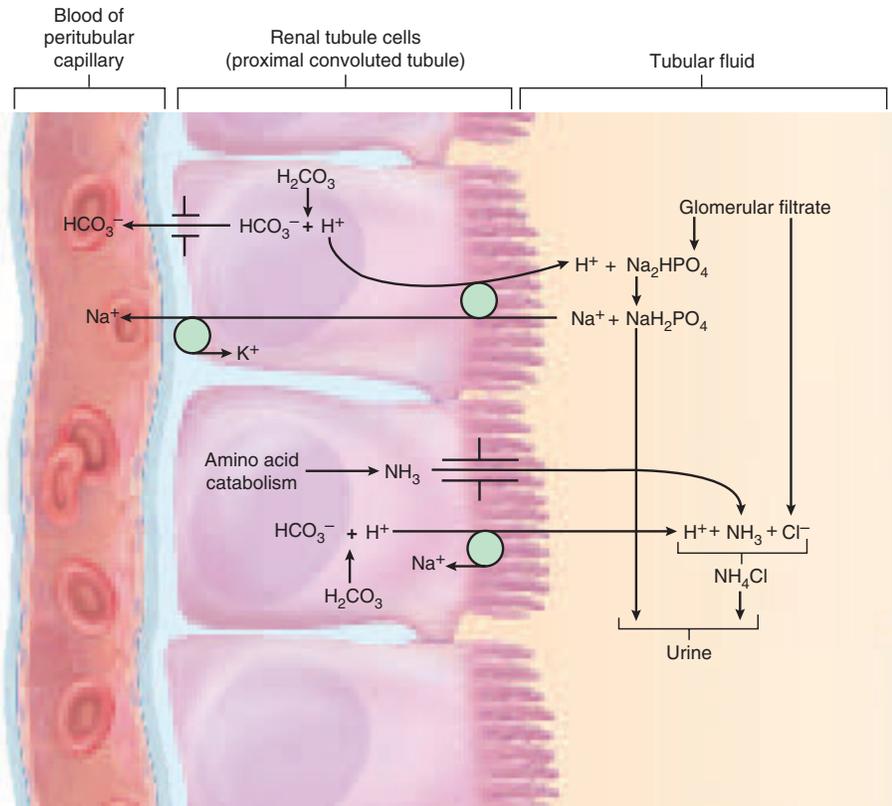Acid–Base Balance

Text

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Figure 24.10 **Mechanisms of Buffering Acid in the Urine.** Reactions in the tubule cells are the same as in figure 24.9 but are simplified in this diagram. The essential differences are the buffering mechanisms shown in the tubular fluid.

Disorders of Acid-Base Balance

At pH 7.4, the ECF has a 20:1 ratio of HCO_3^- to H_2CO_3 (fig. 24.11). If the relative amount of H_2CO_3 rises higher than this, it tips the balance to a lower pH. If the pH falls below 7.35, a state of **acidosis** exists. An excess of HCO_3^-, by contrast, tips the balance to a higher pH. A pH above 7.45 is a state of **alkalosis.** Either of these imbalances has potentially fatal effects. A person cannot live more than a few hours if the blood pH is below 7.0 or above 7.7; a pH below 6.8 or above 8.0 is quickly fatal.

In acidosis, H^+ diffuses down its concentration gradient into the cells, and to maintain electrical balance, K^+ diffuses out (fig. 24.12a). The H^+ is buffered by intracellular proteins, so this exchange results in a net loss of cations from the cell. This makes the resting membrane potential more negative than usual (hyperpolarized) and makes nerve and muscle cells more difficult to stimulate. This is why acidosis depresses the central nervous system and causes such symptoms as confusion, disorientation, and coma.

In alkalosis, the extracellular H^+ concentration is low. Hydrogen ions diffuse out of the cells and K^+ diffuses in to replace them (fig. 24.12b). The net gain in positive intracellular charges shifts the membrane potential closer to firing level and makes the nervous system hyperexcitable. Neurons fire spontaneously and overstimulate skeletal muscles, causing muscle spasms, tetany, convulsions, or respiratory paralysis.

Acid-base imbalances fall into two categories, respiratory and metabolic (table 24.3). **Respiratory acidosis** occurs when the rate of alveolar ventilation fails to keep pace with the body's rate of CO_2 production. Carbon dioxide accumulates in the ECF and lowers its pH. **Respiratory alkalosis** results from hyperventilation, in which CO_2 is eliminated faster than it is produced.

Metabolic acidosis can result from increased production of organic acids, such as lactic acid in anaerobic fermentation and ketone bodies in alcoholism and diabetes mellitus. It can also result from the ingestion of acidic drugs such as aspirin or from the loss of base due to chronic diarrhea or overuse of laxatives. Dying persons
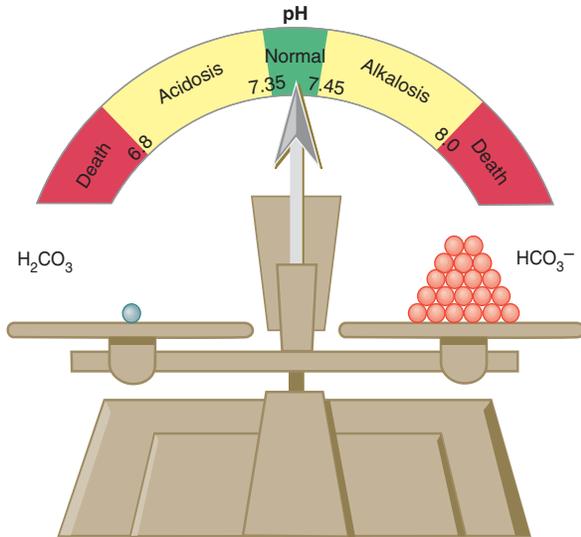
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**Figure 24.11 The Relationship of Carbonic Acid–
Bicarbonate Ratio to pH.** At a normal pH of 7.40, there is a 20:1
ratio of bicarbonate ions (HCO_3^-) to carbonic acid (H_2CO_3) in the blood
plasma. An excess of HCO_3^- tips the balance toward alkalosis, whereas
an excess of H_2CO_3 tips it toward acidosis.

also typically exhibit acidosis. **Metabolic alkalosis** is rare
but can result from overuse of bicarbonates (such as oral
antacids and intravenous bicarbonate solutions) or from
the loss of stomach acid by chronic vomiting.

Compensation for Acid-Base Imbalances

In **compensated** acidosis or alkalosis, either the kidneys
compensate for pH imbalances of respiratory origin, or the
respiratory system compensates for pH imbalances of
metabolic origin. **Uncompensated** acidosis or alkalosis is
a pH imbalance that the body cannot correct without clin-
ical intervention.

In **respiratory compensation,** changes in pulmonary
ventilation correct the pH of the body fluids by expelling
or retaining CO_2. If there is a CO_2 excess (hypercapnia),
pulmonary ventilation increases to expel CO_2 and bring
the blood pH back up to normal. If there is a CO_2 defi-
ciency (hypocapnia), ventilation is reduced to allow CO_2
to accumulate in the blood and lower the pH to normal.

This is very effective in correcting pH imbalances
due to abnormal P_{CO_2} but not very effective in correcting
other causes of acidosis and alkalosis. In diabetic acidosis,

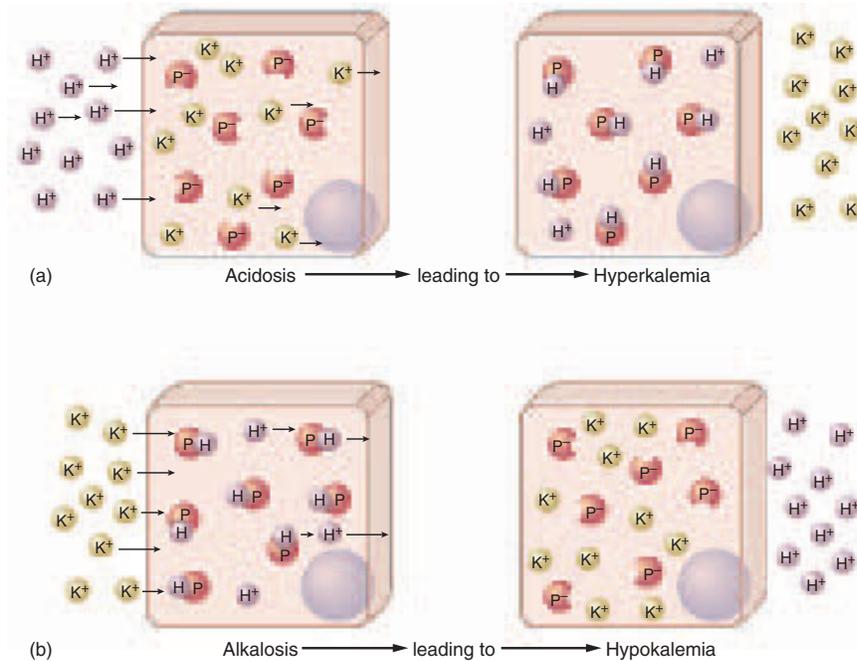**Figure 24.12 The Relationship Between Acid-Base Imbalances and Potassium Imbalances.** (*a*) In acidosis, H⁺ diffuses into the cells and
drives out K⁺, elevating the K⁺ concentration of the ECF. (*b*) In alkalosis, H⁺ diffuses out of the cells and K⁺ diffuses in to replace it, lowering the K⁺
concentration of the ECF.
How would you change figure *a* to show the effect of hyperkalemia on ECF pH?

Chapter 24

Chapter 24

Table 24.3   Some Causes of Acidosis and Alkalosis

	Acidosis	Alkalosis
Respiratory	Hypoventilation, apnea, or respiratory arrest; asthma, emphysema, chronic bronchitis	Hyperventilation due to emotions or oxygen deficiency (as at high altitudes)
Metabolic	Excess production of organic acids, as in diabetes mellitus and long-term anaerobic fermentation; drugs such as aspirin and laxatives; chronic diarrhea	Rare but can result from chronic vomiting or overuse of bicarbonates (antacids)

Table 24.4   Some Relationships Among Fluid, Electrolyte, and Acid-Base Imbalances

Cause	Potential Effect	Reason
Acidosis →	Hyperkalemia	H^+ diffuses into cells and displaces K^+ (see fig. 24.12*a*). As K^+ leaves the ICF, K^+ concentration in the ECF rises.
Hyperkalemia →	Acidosis	Opposite from the above; high K^+ concentration in the ECF causes less K^+ to diffuse out of the cells than normally. H^+ diffuses out to compensate, and this lowers the extracellular pH.
Alkalosis →	Hypokalemia	H^+ diffuses from ICF to ECF. More K^+ remains in the ICF to compensate for the H^+ loss, causing a drop in ECF K^+ concentration (see fig. 24.12*b*).
Hypokalemia →	Alkalosis	Opposite from the above; low K^+ concentration in the ECF causes K^+ to diffuse out of cells. H^+ diffuses in to replace K^+, lowering the H^+ concentration of the ECF and raising its pH.
Acidosis →	Hypochloremia	More Cl^- is excreted as NH_4Cl to buffer the excess acid in the renal tubules, leaving less Cl^- in the ECF.
Alkalosis →	Hyperchloremia	More Cl^- is reabsorbed from the renal tubules, so ingested Cl^- accumulates in the ECF rather than being excreted.
Hyperchloremia →	Acidosis	More H^+ is retained in the blood to balance the excess Cl^-, causing hyperchloremic acidosis.
Hypovolemia →	Alkalosis	More Na^+ is reabsorbed by the kidney. Na^+ reabsorption is coupled to H^+ secretion (see fig. 24.9), so more H^+ is secreted and pH of the ECF rises.
Hypervolemia →	Acidosis	Less Na^+ is reabsorbed, so less H^+ is secreted into the renal tubules. H^+ retained in the ECF causes acidosis.
Acidosis →	Hypocalcemia	Acidosis causes more Ca^{2+} to bind to plasma protein and citrate ions, lowering the concentration of free, ionized Ca^{2+} and causing symptoms of hypocalcemia.
Alkalosis →	Hypercalcemia	Alkalosis causes more Ca^{2+} to dissociate from plasma protein and citrate ions, raising the concentration of free Ca^{2+}.

for example, the lungs cannot reduce the concentration of ketone bodies in the blood, although it can somewhat compensate for the H^+ that they release by increasing pulmonary ventilation and exhausting extra CO_2. The respiratory system can adjust a blood pH of 7.0 back to 7.2 or 7.3 but not all the way back to the normal 7.4. Although the respiratory system has a very powerful buffering effect, its ability to stabilize pH is therefore limited.

Renal compensation is an adjustment of pH by changing the rate of H^+ secretion by the renal tubules. The kidneys are slower to respond to pH imbalances but better at restoring a fully normal pH. Urine usually has a pH of 5 to 6, but in acidosis it may fall as low as 4.5 because of excess H^+, whereas in alkalosis it may rise as high as 8.2

because of excess HCO_3^-. The kidneys cannot act quickly enough to compensate for short-term pH imbalances, such as the acidosis that might result from an asthmatic attack lasting an hour or two, or the alkalosis resulting from a brief episode of emotional hyperventilation. They are effective, however, at compensating for pH imbalances that last for a few days or longer.

In acidosis, the renal tubules increase the rate of H^+ secretion. The extra H^+ in the tubular fluid must be buffered; otherwise, the fluid pH could exceed the limiting pH and H^+ secretion would stop. Therefore, in acidosis, the renal tubules secrete more ammonia to buffer the added H^+, and the amount of ammonium chloride in the urine may rise to 7 to 10 times normal.

Think About It

Suppose you measured the pH and ammonium chloride concentration of urine from a person with emphysema and urine from a healthy individual. How would you expect the two to differ, and why?

In alkalosis, the bicarbonate concentration and pH of the urine are elevated. This is partly because there is more HCO_3^- in the blood and glomerular filtrate and partly because there is not enough H^+ in the tubular fluid to neutralize all the HCO_3^- in the filtrate.

Acid-Base Imbalances in Relation to Electrolyte and Water Imbalances

The foregoing discussion once again stresses a point made early in this chapter—we cannot understand or treat imbalances of water, electrolyte, or acid-base balance in isolation from each other, because each of these frequently affects the other two. Table 24.4 itemizes and explains a few of these interactions. This is by no means a complete list of how fluid, electrolytes, and pH affect each other, but it does demonstrate their interdependence. Note that many of these relationships are reciprocal—for example, acidosis can cause hyperkalemia, and conversely, hyperkalemia can cause acidosis.

Before You Go On

Answer the following questions to test your understanding of the preceding section.

11. Write two chemical equations that show how the bicarbonate buffer system compensates for acidosis and alkalosis and two equations that show how the phosphate buffer system compensates for these imbalances.
12. Why are phosphate buffers more effective in the cytoplasm than in the blood plasma?
13. Renal tubules cannot reabsorb HCO_3^-, and yet HCO_3^- concentration in the tubular fluid falls while in the blood plasma it rises. Explain this apparent contradiction.
14. In acidosis, the renal tubules secrete more ammonia. Why?

Insight 24.2   Clinical Application

Fluid Replacement Therapy

One of the most significant problems in the treatment of seriously ill patients is the restoration and maintenance of proper fluid volume, composition, and distribution among the fluid compartments. Fluids may be administered to replenish total body water, restore blood volume and pressure, shift water from one fluid compartment to another, or restore and maintain electrolyte and acid-base balance.

Drinking water is the simplest method of fluid replacement, but it does not replace electrolytes. Heat exhaustion can occur when you lose water and salt in the sweat and replace the fluid by drinking plain water. Broths, juices, and isotonic sports drinks such as Gatorade replace water, carbohydrates, and electrolytes.

If a patient cannot take fluids by mouth, they must be administered by alternative routes. Some can be given by enema and absorbed through the colon. All routes of fluid administration other than the digestive tract are called *parenteral*[6] routes. The most common of these is the intravenous (I.V.) route, but for various reasons, including inability to find a suitable vein, fluids are sometimes given by subcutaneous (sub-Q), intramuscular (I.M.), or other parenteral routes. Many kinds of sterile solutions are available to meet the fluid replacement needs of different patients.

In cases of extensive blood loss, there may not be time to type and cross-match blood for a transfusion. The more urgent need is to replenish blood volume and pressure. *Normal saline* (isotonic, 0.9% NaCl) is a relatively quick and simple way to raise blood volume while maintaining normal osmolarity, but it has significant shortcomings. It takes three to five times as much saline as whole blood to rebuild normal volume because much of the saline escapes the circulation into the interstitial fluid compartment or is excreted by the kidneys. In addition, normal saline can induce hypernatremia and hyperchloremia, because the body excretes the water but retains much of the NaCl. Hyperchloremia can, in turn, produce acidosis. Normal saline also lacks potassium, magnesium, and calcium. Indeed, it dilutes those electrolytes that are already present and creates a risk of cardiac arrest from hypocalcemia. Saline also dilutes plasma albumin and RBCs, creating still greater risks for patients who have suffered extensive blood loss. Nevertheless, the emergency maintenance of blood volume sometimes takes temporary precedence over these other considerations.

Fluid therapy is also used to correct pH imbalances. Acidosis may be treated with *Ringer's lactate solution,* which includes sodium to rebuild ECF volume, potassium to rebuild ICF volume, lactate to balance the cations, and enough glucose to make the solution isotonic. Alkalosis can be treated with potassium chloride. This must be administered very carefully, because potassium ions can cause painful venous spasms, and even a small potassium excess can cause cardiac arrest. High-potassium solutions should never be given to patients in renal failure or whose renal status is unknown, because in the absence of renal excretion of potassium they can bring on lethal hyperkalemia. Ringer's lactate or potassium chloride also must be administered very cautiously, with close monitoring of blood pH, to avoid causing a pH imbalance opposite the one that was meant to be corrected. Too much Ringer's lactate causes alkalosis and too much KCl causes acidosis.

Plasma volume expanders are hypertonic solutions or colloids that are retained in the bloodstream and draw interstitial water into it by osmosis. They include albumin, sucrose, mannitol, and dextran. Plasma expanders are also used to combat hypotonic hydration by drawing water out of swollen cells, averting such problems as seizures and coma. A plasma expander can draw several liters of water out of the intracellular compartment within a few minutes.

Patients who cannot eat are often given isotonic 5% dextrose (glucose). A fasting patient loses as much as 70 to 85 g of protein per day from the tissues as protein is broken down to fuel the metabolism. Giving 100 to 150 g of I.V. glucose per day reduces this by half and is said to have a *protein-sparing effect.* More than glucose is needed in some cases—for example, if a patient has not eaten for several days and cannot be fed by nasogastric tube (due to lesions of the digestive tract, for example) or if large amounts of nutrients are needed for tissue repair following severe trauma, burns, or infections. In *total parenteral nutrition (TPN),* or *hyperalimentation,*[7] a patient is provided with complete I.V. nutritional support, including a protein hydrolysate (amino acid

Chapter 24

mixture), vitamins, electrolytes, 20% to 25% glucose, and on alternate days, a fat emulsion.

The water from parenteral solutions is normally excreted by the kidneys. If the patient has renal insufficiency, however, excretion may not keep pace with intake, and there is a risk of hypotonic hydration. Intravenous fluids are usually given slowly, by *I.V. drip,* to avoid abrupt changes or overcompensation for the patient's condition. In addition to pH, the patient's pulse rate, blood pressure, hematocrit, and plasma electrolyte concentrations are monitored, and the patient is examined periodically for respiratory sounds indicating pulmonary edema.

The delicacy of fluid replacement therapy underscores the close relationships among fluids, electrolytes, and pH. It is dangerous to manipulate any one of these variables without close attention to the others. Parenteral fluid therapy is usually used for persons who are seriously ill. Their homeostatic mechanisms are already compromised and leave less room for error than in a healthy person.

[6]*para* = beside + *enter* = intestine
[7]*hyper* = above normal + *aliment* = nourishment

Chapter Review

Review of Key Concepts

Water Balance (p. 916)

1. The young adult male body contains about 40 L of water. About 65% is in the intracellular fluid (ICF) and 35% in the extracellular fluid (ECF).
2. Water moves osmotically from one fluid compartment to another so that osmolarities of the ECF and ICF seldom differ.
3. In a state of water balance, average daily fluid gains and losses are equal (typically about 2,500 mL each). Water is gained from the metabolism and by ingestion of food and drink; water is lost in urine, feces, expired breath, sweat, and by cutaneous transpiration.
4. Fluid intake is governed mainly by the sense of thirst, controlled by the *thirst center* of the hypothalamus. This center responds to angiotensin II, ADH, and signals from *osmoreceptor* neurons that monitor blood osmolarity.
5. Long-term satiation of thirst depends on hydration of the blood, although the sense of thirst is briefly suppressed by wetting and cooling of the mouth and filling of the stomach.
6. Fluid loss is governed mainly by the factors that control urine output. ADH, for example, is secreted in response to dehydration and reduces urine output.
7. *Fluid deficiency* occurs when fluid output exceeds intake. In a form of fluid deficiency called *volume depletion (hypovolemia),* total body water is reduced but its osmolarity remains normal, because

proportionate amounts of water and salt are lost. In the other form, true *dehydration,* volume is reduced and osmolarity is elevated because the body has lost more water than salt. Severe fluid deficiency can result in circulatory shock and death.
8. *Fluid excess* occurs in two forms called *volume excess* (retention of excess fluid with normal osmolarity) and *hypotonic hydration* (retention of more water than salt, so osmolarity is low).
9. *Fluid sequestration* is a state in which total body water may be normal, but the water is maldistributed in the body. *Edema* and *pleural effusion* are examples of fluid sequestration.

Electrolyte Balance (p. 921)

1. Sodium is the major cation of the ECF and is important in osmotic and fluid balance, nerve and muscle activity, cotransport, acid-base buffering, and heat generation.
2. Aldosterone promotes Na^+ reabsorption. ADH reduces Na^+ concentration by promoting water reabsorption independently of Na^+. Atrial natriuretic peptide promotes Na^+ excretion.
3. A Na^+ excess *(hypernatremia)* tends to cause water retention, hypertension, and edema. A Na^+ deficiency *(hyponatremia)* is usually a result of hypotonic hydration.
4. Potassium is the major cation of the ICF. It is important for the same reasons as Na^+ and is a cofactor for some enzymes.

5. Aldosterone promotes K^+ excretion.
6. A K^+ excess *(hyperkalemia)* tends to cause nerve and muscle dysfunction, including cardiac arrest. A K^+ deficiency *(hypokalemia)* inhibits nerve and muscle function.
7. Chloride ions are the major anions of the ECF. They are important in osmotic balance, formation of stomach acid, and the chloride shift mechanism in respiratory and renal function.
8. Cl^- follows Na^+ and other cations and is regulated as a side effect of Na^+ homeostasis. The primary effect of chloride imbalances (*hyper-* and *hypochloremia*) is a pH imbalance.
9. Calcium is necessary for muscle contraction, neurotransmission and other cases of exocytosis, blood clotting, some hormone actions, and bone and tooth formation.
10. Calcium homeostasis is regulated by parathyroid hormone, calcitonin, and calcitriol (see chapter 7).
11. Hypercalcemia causes muscular weakness, depressed reflexes, and cardiac arrhythmia. Hypocalcemia causes potentially fatal muscle tetany.
12. Inorganic phosphate (P_i) is a mixture of PO_4^{3-}, HPO_4^{2-}, and $H_2PO_4^-$ ions. P_i is required for the synthesis of nucleic acids, phospholipids, ATP, GTP, and cAMP; it activates many metabolic pathways by phosphorylating such substances as enzymes and glucose; and it is an important acid-base buffer.
13. Phosphate levels are regulated by parathyroid hormone, but phosphate

imbalances are not as critical as imbalances of other electrolytes.

Acid-Base Balance (p. 926)

1. The pH of the ECF is normally maintained between 7.35 and 7.45.
2. pH is determined largely by the tendency of weak and strong acids to give up H^+ to solution, and weak and strong bases to absorb H^+.
3. A *buffer* is any system that resists changes in pH by converting a strong acid or base to a weak one. The *physiological buffers* are the urinary and respiratory systems; the *chemical buffers* are the bicarbonate, phosphate, and protein buffer systems.
4. The respiratory system buffers pH by adjusting pulmonary ventilation. Reduced ventilation allows CO_2 to accumulate in the blood and lower its pH by the reaction $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+$ (generating the H^+ that lowers the pH). Increased ventilation expels CO_2, reversing this reaction, lowering H^+ concentration, and raising the pH.
5. The kidneys neutralize more acid or base than any other buffer system. They secrete H^+ into the tubular fluid, where it binds to chemical buffers and is voided from the body in the urine.
6. This H^+ normally neutralizes all the HCO_3^- in the tubular fluid, making the urine bicarbonate-free. Excess H^+ in the tubular fluid can be buffered by phosphate and ammonia.
7. Acidosis is a pH < 7.35. *Respiratory acidosis* occurs when pulmonary gas exchange is insufficient to expel CO_2 as fast as the body produces it. *Metabolic acidosis* is the result of lactic acid or ketone accumulation, ingestion of acidic drugs such as aspirin, or loss of base in such cases as diarrhea.
8. Alkalosis is a pH > 7.45. *Respiratory alkalosis* results from hyperventilation. *Metabolic alkalosis* is rare but can be caused by overuse of antacids or loss of stomach acid through vomiting.
9. *Uncompensated* acidosis or alkalosis is a pH imbalance that the body's homeostatic mechanisms cannot correct on their own; it requires clinical intervention.
10. *Compensated* acidosis or alkalosis is an imbalance that the body's homeostatic mechanisms can correct. *Respiratory compensation* is correction of the pH through changes in pulmonary ventilation. *Renal compensation* is correction of pH by changes in H^+ secretion by the kidneys.
11. Water, electrolyte, and acid-base imbalances are deeply interconnected; an imbalance in one area can cause or result from an imbalance in another (see table 24.4).

Selected Vocabulary

fluid compartment 916
water balance 916
hypovolemia 919
dehydration 919

volume excess 920
hypotonic hydration 920
hyper- and hyponatremia 923

hyper- and hypokalemia 924
hyper- and hypochloremia 925
hyper- and hypocalcemia 926

buffer 927
acidosis 930
alkalosis 930

Chapter 24

Testing Your Recall

1. The greatest percentage of the body's water is in
   a. the blood plasma.
   b. the lymph.
   c. the intracellular fluid.
   d. the interstitial fluid.
   e. the extracellular fluid.

2. Hypertension is likely to increase the secretion of
   a. atrial natriuretic peptide.
   b. antidiuretic hormone.
   c. bicarbonate ions.
   d. aldosterone.
   e. ammonia.

3. _____ increases water reabsorption without increasing sodium reabsorption.
   a. Antidiuretic hormone
   b. Aldosterone
   c. Atrial natriuretic peptide
   d. Parathyroid hormone
   e. Calcitonin

4. Hypotonic hydration can result from
   a. ADH hypersecretion.
   b. ADH hyposecretion.
   c. aldosterone hypersecretion.
   d. aldosterone hyposecretion.
   e. *a* and *d* only.

5. Tetanus is most likely to result from
   a. hypernatremia.
   b. hypokalemia.
   c. hyperkalemia.
   d. hypocalcemia.
   e. *c* and *d* only.

6. The principal determinant of intracellular osmolarity and cellular volume is
   a. protein.
   b. phosphate.
   c. potassium.
   d. sodium.
   e. chloride.

7. Increased excretion of ammonium chloride in the urine most likely indicates
   a. hypercalcemia.
   b. hyponatremia.
   c. hypochloremia.
   d. alkalosis.
   e. acidosis.

8. The most effective buffer in the intracellular fluid is
   a. phosphate.
   b. protein.
   c. bicarbonate.
   d. carbonic acid.
   e. ammonia.

9. Tubular secretion of hydrogen is directly linked to
   a. tubular secretion of potassium.
   b. tubular secretion of sodium.
   c. tubular reabsorption of potassium.
   d. tubular reabsorption of sodium.
   e. tubular secretion of chloride.

10. Hyperchloremia is most likely to result in
    a. alkalosis.
    b. acidosis.
    c. hypernatremia.
    d. hyperkalemia.
    e. hypovolemia.

11. The most abundant cation in the ECF is _____.

12. The most abundant cation in the ICF is _____.

13. Water produced by the body's chemical reactions is called _____.

14. The skin loses water by two processes, sweating and _____.

15. Any abnormal accumulation of fluid in a particular place in the body is called _____.

16. An excessive concentration of potassium ions in the blood is called _____.

17. A deficiency of sodium ions in the blood is called _____.

18. A blood pH of 7.2 caused by inadequate pulmonary ventilation would be classified as _____.

19. Tubular secretion of hydrogen ions would cease if the acidity of the tubular fluid fell below a value called the _____.

20. Long-term satiation of thirst depends on a reduction of the _____ of the blood.

Answers in Appendix B

True or False

Determine which five of the following statements are false, and briefly explain why.

1. Hypokalemia lowers the resting membrane potentials of nerve and muscle cells and makes them less excitable.

2. Aldosterone promotes sodium and water retention and can therefore greatly increase blood pressure.

3. Injuries that rupture a lot of cells tend to elevate the K^+ concentration of the ECF.

4. It is possible for a person to suffer circulatory shock even without losing a significant amount of fluid from the body.

5. Parathyroid hormone promotes calcium and phosphate reabsorption by the kidneys.

6. The bicarbonate system buffers more acid than any other chemical buffer.

7. The more sodium the renal tubules reabsorb, the more hydrogen ion they secrete into the tubular fluid.

8. The body does not compensate for respiratory acidosis by increasing the respiratory rate.

9. In true dehydration, the body fluids remain isotonic although total body water is reduced.

10. Aquaporins regulate the rate of water reabsorption in the proximal convoluted tubule.

Answers in Appendix B

Testing Your Comprehension

1. A duck hunter is admitted to the hospital with a shotgun injury to the abdomen. He has suffered extensive blood loss but is conscious. He complains of being intensely thirsty. Explain the physiological mechanism connecting his injury to his thirst.

2. A woman living at poverty level finds bottled water at the grocery store next to the infant formula. The label on the water states that it is made especially for infants, and she construes this to mean that it can be used as a nutritional supplement. The water is much cheaper than formula, so she gives her baby several ounces of bottled water a day as a substitute for formula. After several days the baby has seizures and is taken to the hospital, where it is found to have edema, acidosis, and a plasma sodium concentration of 116 mEq/L. The baby is treated with anticonvulsants followed by normal saline and recovers. Explain each of the signs.

3. Explain why the respiratory and urinary systems are both necessary for the bicarbonate buffer system to work effectively in the blood plasma.

4. The left column indicates some increases or decreases in blood plasma values. In the right column, replace the question mark with an up or down arrow to indicate the expected effect. Explain each effect.

Cause	Effect
a. ↑ H_2O	? Na^+
b. ↑ Na^+	? Cl^-
c. ↓ K^+	? H^+
d. ↑ H^+	? K^+
e. ↓ Ca^{2+}	? PO_4^{3-}

5. A 4-year-old child is caught up in tribal warfare in Africa. In a refugee camp, the only drinking water is from a sewage-contaminated pond. The child soon develops severe diarrhea and dies 10 days later of cardiac arrest. Explain the possible physiological cause(s) of his death.

Answers at the Online Learning Center

Answers to Figure Legend Questions

24.1   The tissue fluid
24.7   Ingestion of water

24.9   It would decrease.

24.12   Reverse both arrows to point to the left.

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Chapter 24