CHAPTER 25

Acid-Base Balance

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CHAPTER OUTLINE

KEY CONCEPTS

1. The body is constantly threatened by acid resulting from diet and metabolism. The stability of blood pH is maintained by the concerted action of chemical buffers, the lungs, and the kidneys.
2. Numerous chemical buffers (e.g., HCO_3^-/CO_2, phosphates, proteins) work together to minimize pH changes in the body. The concentration ratio (base/acid) of any buffer pair, together with the pK of the acid, automatically defines the pH.
3. The bicarbonate/CO_2 buffer pair is effective in buffering in the body because its components are present in large amounts and the system is open.
4. The respiratory system influences plasma pH by regulating the P_{CO_2} by changing the level of alveolar ventilation. The kidneys influence plasma pH by getting rid of acid or base in the urine.
5. Renal acidification involves three processes: reabsorption of filtered HCO_3^-, excretion of titratable acid, and excretion of ammonia. New HCO_3^- is added to the plasma and replenishes depleted HCO_3^- when titratable acid (normally mainly $H_2PO_4^-$) and ammonia (as NH_4^+) are excreted.
6. The stability of intracellular pH is ensured by membrane transport of H^+ and HCO_3^-, by intracellular buffers (mainly proteins and organic phosphates), and by metabolic reactions.
7. Respiratory acidosis is an abnormal process characterized by an accumulation of CO_2 and a fall in arterial blood pH. The kidneys compensate by increasing the excretion of H^+ in the urine and adding new HCO_3^- to the blood, thereby, diminishing the severity of the acidemia.
8. Respiratory alkalosis is an abnormal process characterized by an excessive loss of CO_2 and a rise in pH. The kidneys compensate by increasing the excretion of filtered HCO_3^-, thereby, diminishing the alkalemia.
9. Metabolic acidosis is an abnormal process characterized by a gain of acid (other than H_2CO_3) or a loss of HCO_3^-. Respiratory compensation is hyperventilation, and renal compensation is an increased excretion of H^+ bound to urinary buffers (ammonia, phosphate).
10. Metabolic alkalosis is an abnormal process characterized by a gain of strong base or HCO_3^- or a loss of acid (other than H_2CO_3). Respiratory compensation is hypoventilation, and renal compensation is an increased excretion of HCO_3^-.
11. The plasma anion gap is equal to the plasma $[Na^+] - [Cl^-] - [HCO_3^-]$ and is most useful in narrowing down possible causes of metabolic acidosis.

Every day, metabolic reactions in the body produce and consume many moles of hydrogen ions (H^+s). Yet, the $[H^+]$ of most body fluids is very low (in the nanomolar range) and is kept within narrow limits. For example, the $[H^+]$ of arterial blood is normally 35 to 45 nmol/L (pH 7.45 to 7.35). Normally the body maintains acid-base balance; inputs and outputs of acids and bases are matched so that $[H^+]$ stays relatively constant both outside and inside cells.

Most of this chapter discusses the regulation of $[H^+]$ in extracellular fluid because ECF is easier to analyze than intracellular fluid and is the fluid used in the clinical evaluation of acid-base balance. In practice, systemic arterial blood is used as the reference for this purpose. Measure-

ments on whole blood with a pH meter give values for the $[H^+]$ of plasma and, therefore, provide an ECF pH measurement.

A REVIEW OF ACID-BASE CHEMISTRY

In this section, we briefly review some principles of acid-base chemistry. We define acid, base, acid dissociation constant, weak and strong acids, pK_a, pH, and the Henderson-Hasselbalch equation and explain buffering. Students who already feel comfortable with these concepts can skip this section.

Acids Dissociate to Release Hydrogen Ions in Solution

An **acid** is a substance that can release or donate H^+; a **base** is a substance that can combine with or accept H^+. When an acid (generically written as HA) is added to water, it dissociates reversibly according to the reaction, $HA \rightleftharpoons H^+ + A^-$. The species A^- is a base because it can combine with a H^+ to form HA. In other words, when an acid dissociates, it yields a free H^+ and its conjugate (meaning "joined in a pair") base.

The Acid Dissociation Constant K_a Shows the Strength of an Acid

At equilibrium, the rate of dissociation of an acid to form $H^+ + A^-$, and the rate of association of H^+ and base A^- to form HA, are equal. The equilibrium constant (K_a), which is also called the ionization constant or acid **dissociation constant**, is given by the expression

$$K_a = \frac{[H^+] \times [A^-]}{[HA]} \quad (1)$$

The higher the acid dissociation constant, the more an acid is ionized and the greater is its strength. Hydrochloric acid (HCl) is an example of a **strong acid**. It has a high K_a and is almost completely ionized in aqueous solutions. Other strong acids include sulfuric acid (H_2SO_4), phosphoric acid (H_3PO_4), and nitric acid (HNO_3).

An acid with a low K_a is a **weak acid**. For example, in a 0.1 mol solution of acetic acid ($K_a = 1.8 \times 10^{-5}$) in water, most (99%) of the acid is nonionized and little (1%) is present as acetate$^-$ and H^+. The acidity (concentration of free H^+) of this solution is low. Other weak acids are lactic acid, carbonic acid (H_2CO_3), ammonium ion (NH_4^+), and dihydrogen phosphate ($H_2PO_4^-$).

pK_a Is a Logarithmic Expression of K_a

Acid dissociation constants vary widely and often are small numbers. It is convenient to convert K_a to a logarithmic form, defining pK_a as

$$pK_a = \log_{10}(1/K_a) = -\log_{10}K_a \quad (2)$$

In aqueous solution, each acid has a characteristic pK_a, which varies slightly with temperature and the ionic strength of the solution. Note that pK_a is *inversely* proportional to acid strength. A strong acid has a high K_a and a low pK_a. A weak acid has a low K_a and a high pK_a.

pH Is Inversely Related to $[H^+]$

$[H^+]$ is often expressed in pH units. The following equation defines pH:

$$pH = \log_{10}(1/[H^+]) = -\log_{10}[H^+] \quad (3)$$

where $[H^+]$ is in mol/L. Note that pH is *inversely* related to $[H^+]$. Each whole number on the pH scale represents a 10-fold (logarithmic) change in acidity. A solution with a pH of 5 has 10 times the $[H^+]$ of a solution with a pH of 6.

The Henderson-Hasselbalch Equation Relates pH to the Ratio of the Concentrations of Conjugate Base and Acid

For a solution containing an acid and its conjugate base, we can rearrange the equilibrium expression (equation 1) as

$$[H^+] = \frac{K_a \times [HA]}{[A^-]} \quad (4)$$

If we take the negative logarithms of both sides,

$$-\log[H^+] = -\log K_a + \log\frac{[A^-]}{[HA]} \quad (5)$$

Substituting pH for $-\log[H^+]$ and pK_a for $-\log K_a$, we get

$$pH = pK_a + \log\frac{[A^-]}{[A]} \quad (6)$$

This equation is known as the **Henderson-Hasselbalch equation**. It shows that the pH of a solution is determined by the pK_a of the acid and the ratio of the concentration of conjugate base to acid.

Buffers Promote the Stability of pH

The stability of pH is protected by the action of buffers. A **pH buffer** is defined as something that *minimizes* the change in pH produced when an acid or base is added. Note that a buffer *does not prevent* a pH change. A **chemical pH buffer** is a mixture of a weak acid and its conjugate base (or a weak base and its conjugate acid). Following are examples of buffers:

Weak Acid		Conjugate Base	
H_2CO_3 (carbonic acid)	$\rightleftharpoons$	$HCO_3^- + H^+$ (bicarbonate)	(7)
$H_2PO_4^-$ (dihydrogen phosphate)	$\rightleftharpoons$	$HPO_4^{2-} + H^+$ (monohydrogen phosphate)	(8)
NH_4^+ (ammonium ion)	$\rightleftharpoons$	$NH_3 + H^+$ (ammonia)	(9)

Generally, the equilibrium expression for a buffer pair can be written in terms of the Henderson-Hasselbalch equation:

$$pH = pK_a + \log \frac{[\text{conjugate base}]}{[\text{acid}]} \qquad (10)$$

For example, for $H_2PO_4^0/HPO_4^{2-}$

$$pH = 6.8 + \log \frac{[HPO_4^{2-}]}{[HPO_4^-]} \qquad (11)$$

The effectiveness of a buffer—how well it reduces pH changes when an acid or base is added—depends on its concentration and its pK_a. A good buffer is present in high concentrations and has a pK_a close to the desired pH.

Figure 25.1 shows a titration curve for the phosphate buffer system. As a strong acid or strong base is progressively added to the solution (shown on the x-axis), the resulting pH is recorded (shown on the y-axis). Going from right to left as strong acid is added, H^+ combines with the basic form of phosphate: $H^+ + HPO_4^{2-} \rightleftharpoons H_2PO_4^-$. Going from left to right as strong base is added, OH^- combines with H^+ released from the acid form of the phosphate buffer: $OH^- + H_2PO_4^- \rightleftharpoons HPO_4^{2-} + H_2O$. These reactions lessen the fall or rise in pH.

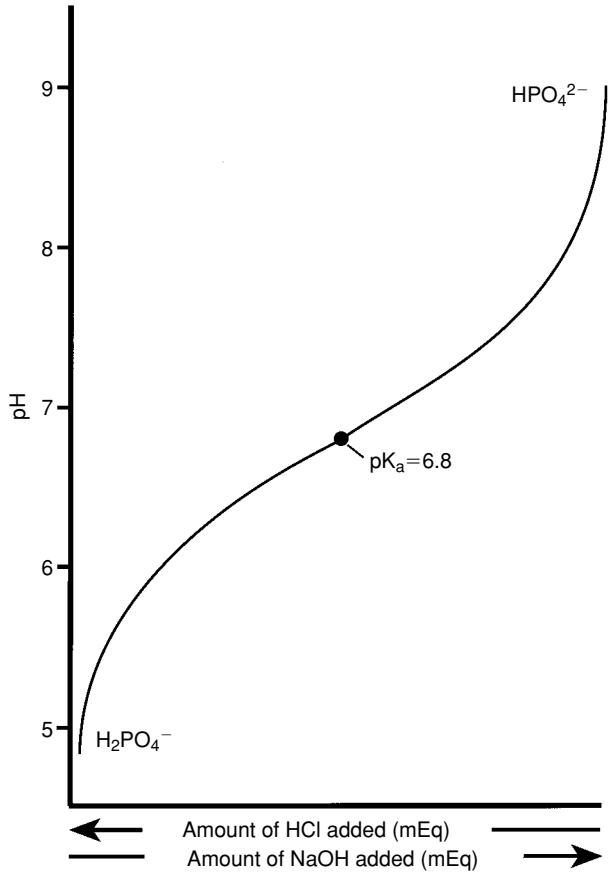

FIGURE 25.1 **A titration curve for a phosphate buffer.** The pK_a for $H_2PO_4^-$ is 6.8. A strong acid (HCl) (right to left) or strong base (NaOH) (left to right) was added and the resulting solution pH recorded (y-axis). Notice that buffering is best (i.e., the change in pH upon the addition of a given amount of acid or base is least) when the solution pH is equal to the pK_a of the buffer.

At the pK_a of the phosphate buffer, the ratio $[HPO_4^{2-}]/[H_2PO_4^-]$ is 1 and the titration curve is flattest (the change in pH for a given amount of an added acid or base is at a minimum). In most cases, pH buffering is effective when the solution pH is within plus or minus one pH unit of the buffer pK_a. Beyond that range, the pH shift that a given amount of acid or base produces may be large, so the buffer becomes relatively ineffective.

PRODUCTION AND REGULATION OF HYDROGEN IONS IN THE BODY

Acids are continuously produced in the body and threaten the normal pH of the extracellular and intracellular fluids. Physiologically speaking, acids fall into two groups: (1) H_2CO_3 (carbonic acid), and (2) all other acids (noncarbonic; also called "nonvolatile" or "fixed" acids). The distinction between these groups occurs because H_2CO_3 is in equilibrium with the volatile gas CO_2, which can leave the body via the lungs. The concentration of H_2CO_3 in arterial blood is, therefore, set by respiratory activity. By contrast, noncarbonic acids in the body are not directly affected by breathing. Noncarbonic acids are buffered in the body and excreted by the kidneys.

Metabolism Is a Constant Source of Carbon Dioxide

A normal adult produces about 300 L of CO_2 daily from metabolism. CO_2 from tissues enters the capillary blood, where it reacts with water to form H_2CO_3, which dissociates instantly to yield H^+ and HCO_3^-: $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$. Blood pH would rapidly fall to lethal levels if the H_2CO_3 formed from CO_2 were allowed to accumulate in the body.

Fortunately, H_2CO_3 produced from metabolic CO_2 is only formed transiently in the transport of CO_2 by the blood and does not normally accumulate. Instead, it is converted to CO_2 and water in the pulmonary capillaries and the CO_2 is expired. In the lungs, the reactions reverse:

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2 \qquad (12)$$

As long as CO_2 is expired as fast as it is produced, arterial blood CO_2 tension, H_2CO_3 concentration, and pH do not change.

Incomplete Carbohydrate and Fat Metabolism Produces Nonvolatile Acids

Normally, carbohydrates and fats are completely oxidized to CO_2 and water. If carbohydrates and fats are *incompletely* oxidized, nonvolatile acids are produced. Incomplete oxidation of carbohydrates occurs when the tissues do not receive enough oxygen, as during strenuous exercise or hem-

orrhagic or cardiogenic shock. In such states, glucose metabolism yields lactic acid (pK_a = 3.9), which dissociates into lactate and H^+, lowering the blood pH. Incomplete fatty acid oxidation occurs in uncontrolled diabetes mellitus, starvation, and alcoholism and produces ketone body acids (acetoacetic and β-hydroxybutyric acids). These acids have pK_a values around 4 to 5. At blood pH, they mostly dissociate into their anions and H^+, making the blood more acidic.

Protein Metabolism Generates Strong Acids

The metabolism of dietary proteins is a major source of H^+. The oxidation of proteins and amino acids produces strong acids such as H_2SO_4, HCl, and H_3PO_4. The oxidation of sulfur-containing amino acids (methionine, cysteine, cystine) produces H_2SO_4, and the oxidation of cationic amino acids (arginine, lysine, and some histidine residues) produces HCl. H_3PO_4 is produced by the oxidation of phosphorus-containing proteins and phosphoesters in nucleic acids.

On a Mixed Diet, Net Acid Gain Threatens pH

A diet containing both meat and vegetables results in a net production of acids, largely from protein oxidation. To some extent, acid-consuming metabolic reactions balance H^+ production. Food also contains basic anions, such as citrate, lactate, and acetate. When these are oxidized to CO_2 and water, H^+ ions are consumed (or, amounting to the same thing, HCO_3^- is produced). The balance of acid-forming and acid-consuming metabolic reactions results in a net production of about 1 mEq H^+/kg body weight/day in an adult person who eats a mixed diet. Persons who are vegetarians generally have less of a dietary acid burden and a more alkaline urine pH than nonvegetarians because most fruits and vegetables contain large amounts of organic anions that are metabolized to HCO_3^-. The body generally has to dispose of more or less nonvolatile acid, a function performed by the kidneys.

Whether a particular food has an acidifying or an alkalinizing effect depends on if and how its constituents are metabolized. Cranberry juice has an acidifying effect because of its content of benzoic acid, an acid that cannot be broken down in the body. Orange juice has an alkalinizing effect, despite its acidic pH of about 3.7, because it contains citrate, which is metabolized to HCO_3^-. The citric acid in orange juice is converted to CO_2 and water and has only a transient effect on blood pH and no effect on urine pH.

Many Buffering Mechanisms Protect and Stabilize Blood pH

Despite constant threats to acid-base homeostasis, a healthy person maintains a normal blood pH. Figure 25.2 shows some of the ways in which blood pH is kept at normal levels despite the daily net acid gain. The key buffering agents are chemical buffers, along with the lungs and kidneys.

1) Chemical buffering. Chemical buffers in extracellular and intracellular fluids and in bone are the first line of defense of blood pH. Chemical buffering minimizes a change in pH but does not remove acid or base from the body.

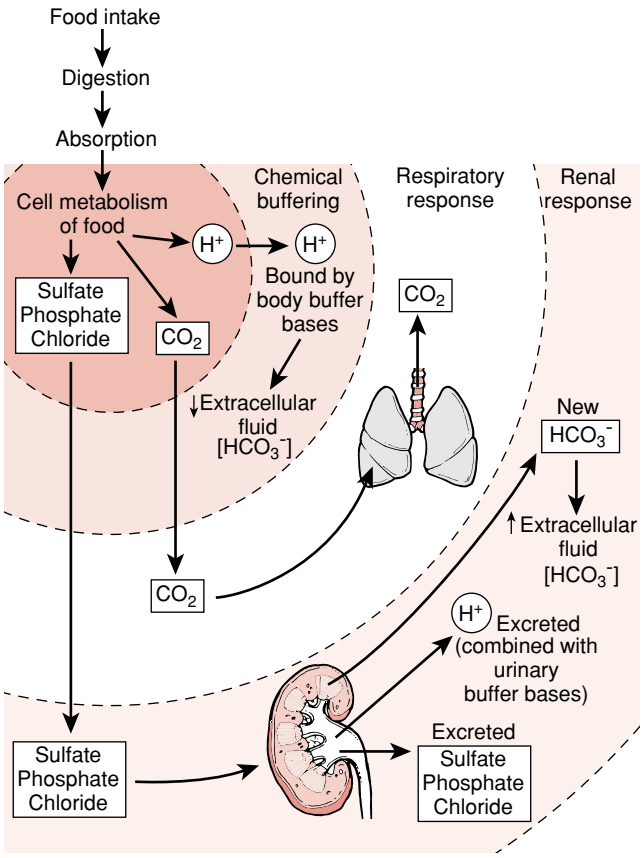

FIGURE 25.2 The maintenance of normal blood pH by chemical buffers, the respiratory system, and the kidneys. On a mixed diet, pH is threatened by the production of strong acids (sulfuric, hydrochloric, and phosphoric) mainly as a result of protein metabolism. These strong acids are buffered in the body by chemical buffer bases, such as ECF HCO_3^-. The kidneys eliminate hydrogen ions (combined with urinary buffers) and anions in the urine. At the same time, they add new HCO_3^- to the ECF, to replace the HCO_3^- consumed in buffering strong acids. The respiratory system disposes of CO_2.

2) Respiratory response. The respiratory system is the second line of defense of blood pH. Normally, breathing removes CO_2 as fast as it forms. Large loads of acid stimulate breathing (respiratory compensation), which removes CO_2 from the body and lowers the $[H_2CO_3]$ in arterial blood, reducing the acidic shift in blood pH.

3) Renal response. The kidneys are the third line of defense of blood pH. Although chemical buffers in the body can bind H^+ and the lungs can change $[H_2CO_3]$ of blood, the burden of removing excess H^+ falls directly on the kidneys. Hydrogen ions are excreted in combination with urinary buffers. At the same time, the kidneys add new HCO_3^- to the ECF to replace HCO_3^- used to buffer strong acids. The kidneys also excrete the anions (phosphate, chloride, sulfate) that are liberated from strong acids. The kidneys affect blood pH more slowly than other buffering mechanisms in the body; full renal compensation may take 1 to 3 days.

CHEMICAL REGULATION OF PH

The body contains many conjugate acid-base pairs that act as chemical buffers (Table 25.1). In the ECF, the main chemical buffer pair is HCO_3^-/CO_2. Plasma proteins and inorganic phosphate are also ECF buffers. Cells have large buffer stores, particularly proteins and organic phosphate compounds. HCO_3^- is present in cells, although at a lower concentration than in ECF. Bone contains large buffer stores, specifically phosphate and carbonate salts.

Chemical Buffers Are the First to Defend pH

When an acid or base is added to the body, the buffers just mentioned bind or release H^+, minimizing the change in pH. Buffering in ECF occurs rapidly, in minutes. Acids or bases also enter cells and bone, but this generally occurs more slowly, over hours, allowing cell buffers and bone to share in buffering.

A pK_a of 6.8 Makes Phosphate a Good Buffer

The pK_a for phosphate, $H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$, is 6.8, close to the desired blood pH of 7.4, so phosphate is a good buffer. In the ECF, phosphate is present as inorganic phosphate. Its concentration, however, is low (about 1 mmol/L), so it plays a minor role in extracellular buffering.

Phosphate is an important intracellular buffer, however, for two reasons. First, cells contain large amounts of phosphate in such organic compounds as adenosine triphosphate (ATP), adenosine diphosphate (ADP), and creatine phosphate. Although these compounds primarily function in energy metabolism, they also act as pH buffers. Second, intracellular pH is generally lower than the pH of ECF and is closer to the pK_a of phosphate. (The cytosol of skeletal muscle, for example, has a pH of 6.9.) Phosphate is, thus, more effective in this environment than in one with a pH of 7.4. Bone has large phosphate salt stores, which also help in buffering.

TABLE 25.1 Major Chemical pH Buffers in the Body

Buffer	Reaction
Extracellular fluid	
Bicarbonate/CO_2	$CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$
Inorganic phosphate	$H_2PO_4^- \leftrightarrows H^+ + HPO_4^{2-}$
Plasma proteins (Pr)	$HPr \leftrightarrows H^+ + Pr^-$
Intracellular fluid	
Cell proteins (e.g., hemoglobin, Hb)	$HHb \leftrightarrows H^+ + Hb^-$
Organic phosphates	$Organic\text{-}HPO_4^- \leftrightarrows H^+ + organic\text{-}PO_4^{2-}$
Bicarbonate/CO_2	$CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$
Bone	
Mineral phosphates	$H_2PO_4^- \leftrightarrows H^+ + HPO_4^{2-}$
Mineral carbonates	$HCO_3^- \leftrightarrows H^+ + CO_3^{2-}$

Proteins Are Excellent Buffers

Proteins are the largest buffer pool in the body and are excellent buffers. Proteins can function as both acids and bases, so they are **amphoteric**. They contain many ionizable groups, which can release or bind H^+. Serum albumin and plasma globulins are the major extracellular protein buffers, present mainly in the blood plasma. Cells also have large protein stores. Recall that the buffering properties of hemoglobin play an important role in the transport of CO_2 and O_2 by the blood (see Chapter 21).

The Bicarbonate/Carbon Dioxide Buffer Pair Is Crucial in pH Regulation

For several reasons, the HCO_3^-/CO_2 buffer pair is especially important in acid-base physiology:

1) Its components are abundant; the concentration of HCO_3^- in plasma or ECF normally averages 24 mmol/L. Although the concentration of dissolved CO_2 is lower (1.2 mmol/L), metabolism provides a nearly limitless supply.

2) Despite a pK of 6.10, a little far from the desired plasma pH of 7.40, it is effective because the system is "open."

3) It is controlled by the lungs and kidneys.

Forms of Carbon Dioxide. CO_2 exists in the body in several different forms: as gaseous CO_2 in the lung alveoli, and as dissolved CO_2, H_2CO_3, HCO_3^-, carbonate (CO_3^{2-}), and carbamino compounds in the body fluids.

CO_3^{2-} is present at appreciable concentrations only in rather alkaline solutions, and so we will ignore it. We will also ignore any CO_2 that is bound to proteins in the carbamino form. The most important forms are gaseous CO_2, dissolved CO_2, H_2CO_3, and HCO_3^-.

The $CO_2/H_2CO_3/HCO_3^-$ Equilibria. Dissolved CO_2 in pulmonary capillary blood equilibrates with gaseous CO_2 in the lung alveoli. Consequently, the partial pressures of CO_2 (P_{CO_2}) in alveolar air and systemic arterial blood are normally identical. The concentration of dissolved CO_2 ($[CO_{2(d)}]$) is related to the P_{CO_2} by Henry's law (see Chapter 21). The solubility coefficient for CO_2 in plasma at 37°C is 0.03 mmol CO_2/L per mm Hg P_{CO_2}. Therefore, $[CO_{2(d)}] = 0.03 \times P_{CO_2}$. If P_{CO_2} is 40 mm Hg, then $[CO_{2(d)}]$ is 1.2 mmol/L.

In aqueous solutions, $CO_{2(d)}$ reacts with water to form H_2CO_3: $CO_{2(d)} + H_2O \rightleftharpoons H_2CO_3$. The reaction to the right is called the **hydration reaction,** and the reaction to the left is called the **dehydration reaction**. These reactions are slow if uncatalyzed. In many cells and tissues, such as the kidneys, pancreas, stomach, and red blood cells, the reactions are catalyzed by **carbonic anhydrase**, a zinc-containing enzyme. At equilibrium, $CO_{2(d)}$ is greatly favored; at body temperature, the ratio of $[CO_{2(d)}]$ to $[H_2CO_3]$ is about 400:1. If $[CO_{2(d)}]$ is 1.2 mmol/L, then $[H_2CO_3]$ equals 3 μmol/L. H_2CO_3 dissociates instantaneously into H^+ and HCO_3^-: $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$. The Henderson-Hasselbalch expression for this reaction is

$$pH = 3.5 + \log \frac{[HCO_3^-]}{[H_2CO_3]} \qquad (13)$$

Note that H_2CO_3 is a fairly strong acid ($pK_a = 3.5$). Its low concentration in body fluids lessens its impact on acidity.

The Henderson-Hasselbalch Equation for HCO_3^-/CO_2. Because $[H_2CO_3]$ is so low and hard to measure and because $[H_2CO_3] = [CO_{2(d)}]/400$, we can use $[CO_{2(d)}]$ to represent the acid in the Henderson-Hasselbalch equation:

$$\begin{aligned} pH &= 3.5 + \log \frac{[HCO_3^-]}{[CO_{2(d)}]/400} \\ &= 3.5 + \log 400 + \log \frac{[HCO_3^-]}{[CO_{2(d)}]} \\ &= 6.1 + \log \frac{[HCO_3^-]}{[CO_{2(d)}]} \end{aligned} \quad (14)$$

We can also use $0.03 \times P_{CO_2}$ in place of $[CO_{2(d)}]$:

$$pH = 6.1 + \log \frac{[HCO3-]}{0.03\ P_{CO_2}} \quad (15)$$

This form of the Henderson-Hasselbalch equation is useful in understanding acid-base problems. Note that the "acid" in this equation appears to be $CO_{2(d)}$, but is really H_2CO_3 "represented" by CO_2. Therefore, this equation is valid only if $CO_{2(d)}$ and H_2CO_3 are in equilibrium with each other, which is usually (but not always) the case.

Many clinicians prefer to work with $[H^+]$ rather than pH. The following expression results if we take antilogarithms of the Henderson-Hasselbalch equation:

$$[H^+] = 24\ P_{CO_2}/[HCO_3^-] \quad (16)$$

In this expression, $[H^+]$ is expressed in nmol/L, $[HCO_3^-]$ in mmol/L or mEq/L, and P_{CO_2} in mm Hg. If P_{CO} is 40 mm Hg and plasma $[HCO_3^-]$ is 24 mmol/L, $[H^+]$ is 40 nmol/L.

An "Open" Buffer System. As previously noted, the pK of the HCO_3^-/CO_2 system (6.10) is far from 7.40, the normal pH of arterial blood. From this, one might view this as a rather poor buffer pair. On the contrary, it is remarkably effective because it operates in an open system; that is, the two buffer components can be added to or removed from the body at controlled rates.

The HCO_3^-/CO_2 system is open in several ways:

1) Metabolism provides an endless source of CO_2, which can replace any H_2CO_3 consumed by a base added to the body.

2) The respiratory system can change the amount of CO_2 in body fluids by hyperventilation or hypoventilation.

3) The kidneys can change the amount of HCO_3^- in the ECF by forming new HCO_3^- when excess acid has been added to the body or excreting HCO_3^- when excess base has been added.

How the kidneys and respiratory system influence blood pH by operating on the HCO_3^-/CO_2 system is described below. For now, the advantages of an open buffer system are best explained by an example (Fig. 25.3). Suppose we have 1 L of blood containing 24 mmol of HCO_3^- and 1.2 mmol of dissolved $CO_{2(d)}$ ($P_{CO_2} = 40$ mm Hg). Using the special form of the Henderson-Hasselbalch equation described above, we find that the pH of the blood is 7.40:

$$\begin{aligned} pH &= 6.10 + \log \frac{[HCO_3^-]}{0.03\ P_{CO_2}} \\ &= 6.10 + \log \frac{[24]}{[1.2]} = 7.40 \end{aligned} \quad (17)$$

Suppose we now add 10 mmol of HCl, a strong acid. HCO_3^- is the major buffer base in the blood plasma (we will neglect the contributions of other buffers). From the reaction $H^+ + HCO_3^- \leftrightharpoons H_2CO_3 \leftrightharpoons H_2O + CO_2$, we predict that the $[HCO_3^-]$ will fall by 10 mmol, and that 10 mmol of $CO_{2(d)}$ will form. If the system were closed and no CO_2 could escape, the new pH would be

$$pH = 6.10 + \log \frac{[24 - 10]}{[1.2 + 10]} = 6.20 \quad (18)$$

This is an intolerably low—indeed a fatal—pH.

Fortunately, however, the system is open and CO_2 can escape via the lungs. If all of the extra CO_2 is expired and the $[CO_{2(d)}]$ is kept at 1.2 mmol/L, the pH would be

$$pH = 6.10 + \log \frac{[24 - 10]}{[1.2]} = 7.17 \quad (19)$$

Although this pH is low, it is compatible with life.

Still another mechanism promotes the escape of CO_2. In the body, an acidic blood pH stimulates breathing, which can make the P_{CO_2} lower than 40 mm Hg. If P_{CO_2} falls to 30 mm Hg ($[CO_{2(d)}] = 0.9$ mmol/L) the pH would be

$$pH = 6.10 + \log \frac{[24 - 10]}{[0.9]} = 7.29 \quad (20)$$

The system is also open at the kidneys and new HCO_3^- can be added to the plasma to correct the plasma $[HCO_3^-]$. Once the pH of the blood is normal, the stimulus for hyperventilation disappears.

Changes in Acid Production May Help Protect Blood pH

Another way in which blood pH may be protected is by changes in endogenous acid production (Fig. 25.4). An increase in blood pH caused by the addition of base to the body results in increased production of lactic acid and ketone body acids, which then reduces the alkaline shift in pH. A decrease in blood pH results in decreased production of lactic acid and ketone body acids, which opposes the acidic shift in pH.

This scenario is especially important when the endogenous production of these acids is high, as occurs during strenuous exercise or other conditions of circulatory inadequacy (lactic acidosis) or during ketosis as a result of uncontrolled diabetes, starvation, or alcoholism. These effects of pH on endogenous acid production result from changes in enzyme

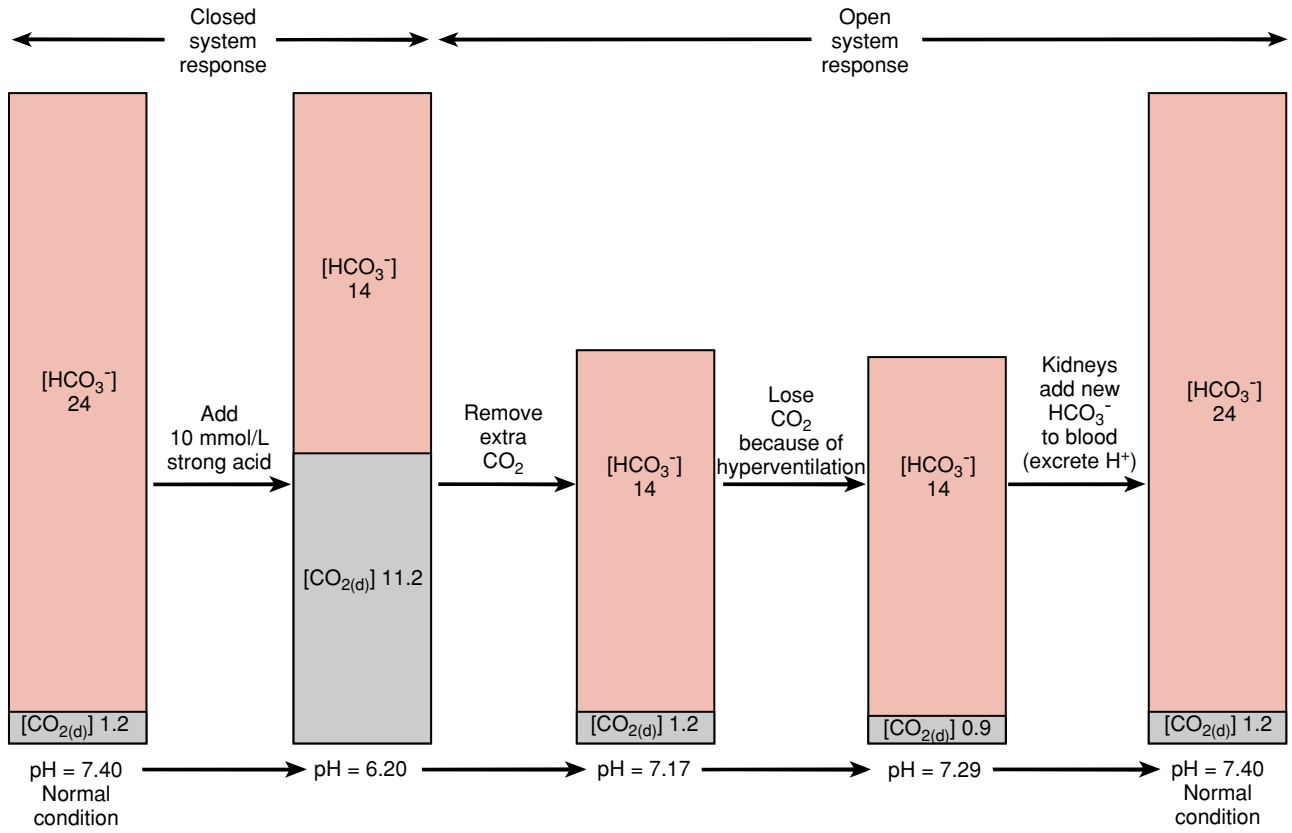

FIGURE 25.3 **The HCO_3^-/CO_2 system.** This system is remarkably effective in buffering added strong acid in the body because it is open. $[HCO_3^-]$ and $[CO_{2(d)}]$ are in mmol/L. See text for details. (Adapted from Pitts RF. Physiology of the Kidney and Body Fluids. 3rd Ed. Chicago: Year Book, 1974.)

activities brought about by the pH changes, and they are part of a negative-feedback mechanism regulating blood pH.

All Buffers Are in Equilibrium With the Same $[H^+]$

We have discussed the various buffers separately but, in the body, they all work together. In a solution containing multiple buffers, all are in equilibrium with the same $[H^+]$. This idea is known as the **isohydric principle** (*isohydric* meaning "same H^+"). For plasma, for example, we can write

$$pH = 6.80 + \log \frac{[HPO_4^{2-}]}{[H_2PO_4^-]}$$

$$= 6.10 + \log \frac{[HCO_3^-]}{0.03\ P_{CO_2}}$$

$$= pK_{protein} + \log \frac{[proteinate^-]}{[H\text{-protein}]} \qquad (21)$$

If an acid or a base is added to such a complex mixture of buffers, all buffers take part in buffering and shift from one form (base or acid) to the other. The relative importance of each buffer depends on its amount, pK, and availability.

The isohydric principle underscores the fact that it is the concentration ratio for any buffer pair, together with its pK, that sets the pH. We can focus on the concentration ratio for one buffer pair and all other buffers will automatically adjust their ratios according to the pH and their pK values.

The rest of this chapter emphasizes the role of the HCO_3^-/CO_2 buffer pair in setting the blood pH. Other buffers, however, are present and active. The HCO_3^-/CO_2 system is emphasized because physiological mechanisms (lungs and kidneys) regulate pH by acting on components of this buffer system.

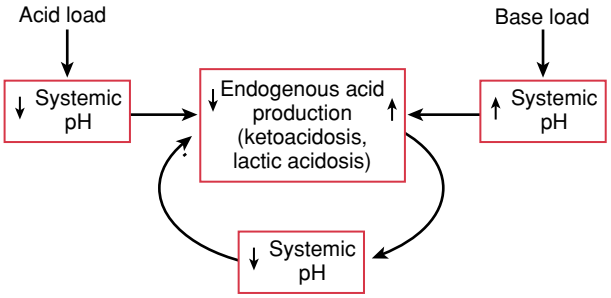

FIGURE 25.4 **Negative-feedback control of endogenous acid production.** The addition of an exogenous acid load or increased endogenous acid production result in a fall in pH, which, in turn, inhibits the production of ketone body acids and lactic acid. A base load, by raising pH, stimulates the endogenous production of acids. This negative-feedback mechanism attenuates changes in blood pH. (From Hood VL, Tannen RL. Protection of acid-base balance by pH regulation of acid production. N Engl J Med 1998;339:819–826.)

RESPIRATORY REGULATION OF PH

Reflex changes in ventilation help to defend blood pH. By changing the P_{CO_2} and, hence, $[H_2CO_3]$ of the blood, the respiratory system can rapidly and profoundly affect blood pH. As discussed in Chapter 22, a fall in blood pH stimulates ventilation, primarily by acting on peripheral chemoreceptors. An elevated arterial blood P_{CO_2} is a powerful stimulus to increase ventilation; it acts on both peripheral and central chemoreceptors, but primarily on the latter. CO_2 diffuses into brain interstitial and cerebrospinal fluids, where it causes a fall in pH that stimulates chemoreceptors in the medulla oblongata. When ventilation is stimulated, the lungs blow off more CO_2, making the blood less acidic. Conversely, a rise in blood pH inhibits ventilation; the consequent rise in blood $[H_2CO_3]$ reduces the alkaline shift in blood pH. Respiratory responses to disturbed blood pH begin within minutes and are maximal in about 12 to 24 hours.

RENAL REGULATION OF PH

The kidneys play a critical role in maintaining acid-base balance. If there is excess acid in the body, they remove H^+, or if there is excess base, they remove HCO_3^-. The usual challenge is to remove excess acid. As we have learned, strong acids produced by metabolism are first buffered by body buffer bases, particularly HCO_3^-. The kidneys then must eliminate H^+ in the urine and restore the depleted HCO_3^-.

Little of the H^+ excreted in the urine is present as free H^+. For example, if the urine has its lowest pH value (pH = 4.5), $[H^+]$ is only 0.03 mEq/L. With a typical daily urine output of 1 to 2 L, the amount of acid the body must dispose of daily (about 70 mEq) obviously is not excreted in the free form. Most of the H^+ combines with urinary buffers to be excreted as titratable acid and as NH_4^+.

Titratable acid is measured from the amount of strong base (NaOH) needed to bring the urine pH back to the pH of the blood (usually, 7.40). It represents the amount of H^+ ions that are excreted, combined with urinary buffers such as phosphate, creatinine, and other bases. The largest component of titratable acid is normally phosphate, that is, $H_2PO_4^-$.

Hydrogen ions secreted by the renal tubules also combine with the free base NH_3 and are excreted as NH_4^+. Ammonia (a term that collectively includes both NH_3 and NH_4^+) is produced by the kidney tubule cells and is secreted into the urine. Because the pK_a for NH_4^+ is high (9.0), most of the ammonia in the urine is present as NH_4^+. For this reason, too, NH_4^+ is not appreciably titrated when titratable acid is measured. Urinary ammonia is measured by a separate, often chemical, method.

Renal Net Acid Excretion Equals the Sum of Urinary Titratable Acid and Ammonia Minus Urinary Bicarbonate

In stable acid-base balance, net acid excretion by the kidneys equals the net rate of H^+ addition to the body by metabolism or other processes, assuming that other routes of loss of acid or base (e.g., gastrointestinal losses) are small and can be neglected, which normally is the case. The net loss of H^+ in the urine can be calculated from the following equation, which shows typical values in the parentheses:

$$\begin{aligned}\text{Renal net acid excretion (70 mEq/day)} = \\ &\text{urinary titratable acid (24 mEq/day)} + \\ &\text{urinary ammonia (48 mEq/day)} - \\ &\text{urinary } HCO_3^- \text{ (2 mEq/day)}\end{aligned} \quad (22)$$

Urinary ammonia (as NH_4^+) ordinarily accounts for about two thirds of the excreted H^+, and titratable acid for about one third. Excretion of HCO_3^- in the urine represents a loss of base from the body. Therefore, it must be subtracted in the calculation of net acid excretion. If the urine contains significant amounts of organic anions, such as citrate, that potentially could have yielded HCO_3^- in the body, these should also be subtracted. Since the amount of free H^+ excreted is negligible, this is omitted from the equation.

Hydrogen Ions Are Added to Urine as It Flows Along the Nephron

As the urine flows along the tubule, from Bowman's capsule on through the collecting ducts, three processes occur: filtered HCO_3^- is reabsorbed, titratable acid is formed, and ammonia is added to the tubular urine. All three processes involve H^+ secretion (urinary acidification) by the tubular epithelium. The nature and magnitude of these processes vary in different nephron segments. Figure 25.5 summarizes measurements of tubular fluid pH along the nephron and shows ammonia movements in various nephron segments.

Acidification in the Proximal Convoluted Tubule. The pH of the glomerular ultrafiltrate, at the beginning of the proximal tubule, is identical to that of the plasma from which it is derived (7.4). H^+ ions are secreted by the proximal tubule epithelium into the tubule lumen; about two thirds of this is accomplished by a Na^+/H^+ exchanger and about one third by H^+-ATPase in the brush border membrane. Tubular fluid pH falls to a value of about 6.7 by the end of the proximal convoluted tubule (see Fig. 25.5).

The drop in pH is modest for two reasons: buffering of secreted H^+ and the high permeability of the proximal tubule epithelium to H^+. The glomerular filtrate and tubule fluid contain abundant buffer bases, especially HCO_3^-, which soak up secreted H^+, minimizing a fall in pH. The proximal tubule epithelium is rather leaky to H^+, so that any gradient from urine to blood, established by H^+ secretion, is soon limited by the diffusion of H^+ out of the tubule lumen into the blood surrounding the tubules

Most of the H^+ ions secreted by the nephron are secreted in the proximal convoluted tubule and are used to bring about the reabsorption of filtered HCO_3^-. Secreted H^+ ions are also buffered by filtered phosphate to form titratable acid. Ammonia is produced by proximal tubule cells, mainly from glutamine. It is secreted into the tubular urine by the diffusion of NH_3, which then combines with a secreted H^+ to form NH_4^+, or via the brush border membrane Na^+/H^+ exchanger, which can operate in a Na^+/NH_4^+ exchange mode.

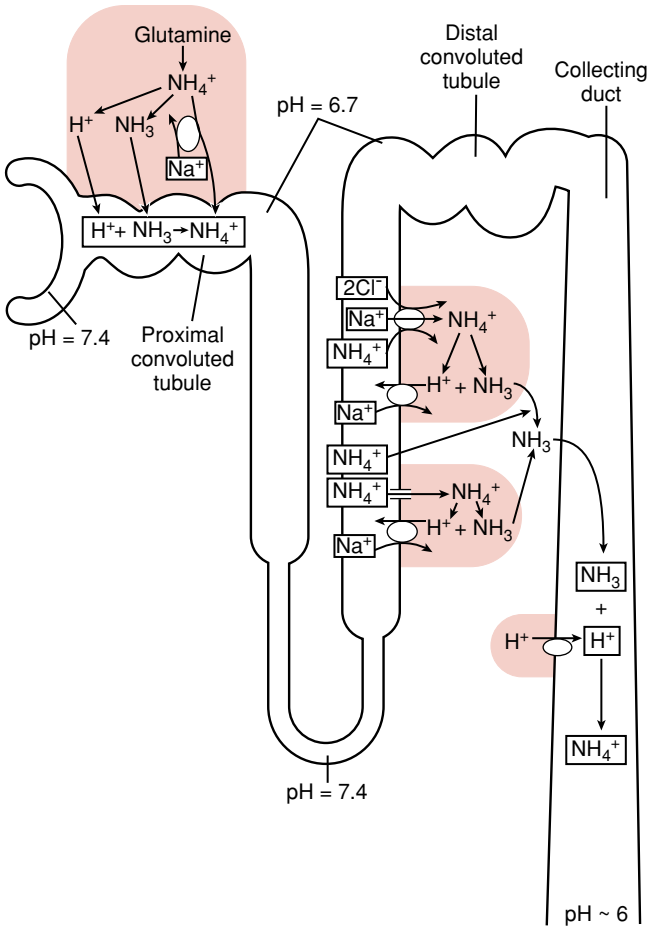

FIGURE 25.5 **Acidification along the nephron.** The pH of tubular urine decreases along the proximal convoluted tubule, rises along the descending limb of the Henle loop, falls along the ascending limb, and reaches its lowest values in the collecting ducts. Ammonia ($=NH_3 + NH_4^+$) is chiefly produced in proximal tubule cells and is secreted into the tubular urine. NH_4^+ is reabsorbed in the thick ascending limb and accumulates in the kidney medulla. NH_3 diffuses into acidic collecting duct urine, where it is trapped as NH_4^+.

Acidification in the Henle Loop. Along the descending limb of the Henle loop, the pH of tubular fluid rises (from 6.7 to 7.4). This rise is explained by an increase in intraluminal $[HCO_3^-]$ caused by water reabsorption. Ammonia is secreted along the descending limb.

The tubular fluid is acidified by secretion of H^+ along the ascending limb via a Na^+/H^+ exchanger. Along the thin ascending limb, ammonia is passively reabsorbed. Along the thick ascending limb, NH_4^+ is mostly actively reabsorbed by the Na-K-2Cl cotransporter in the luminal plasma membrane (NH_4^+ substitutes for K^+). Some NH_4^+ can be reabsorbed via a luminal plasma membrane K^+ channel. Also, some NH_4^+ can be passively reabsorbed between cells in this segment; the driving force is the lumen positive transepithelial electrical potential difference. Ammonia may undergo countercurrent multiplication in the Henle loop, leading to an ammonia concentration gradient in the kidney medulla. The highest concentrations are at the tip of the papilla.

Acidification in the Distal Nephron. The distal nephron (distal convoluted tubule, connecting tubule, and collecting duct) differs from the proximal portion of the nephron in its H^+ transport properties. It secretes far fewer H^+ ions, and they are secreted primarily via an electrogenic H^+-ATPase or an electroneutral H^+/K^+-ATPase. The distal nephron is also lined by "tight" epithelia, so little secreted H^+ diffuses out of the tubule lumen, making steep urine-to-blood pH gradients possible (see Fig. 25.5). Final urine pH is typically about 6, but may be as low as 4.5.

The distal nephron usually almost completely reabsorbs the small quantities of HCO_3^- that were not reabsorbed by more proximal nephron segments. Considerable titratable acid forms as the urine is acidified. Ammonia, which was reabsorbed by the ascending limb of the Henle loop and has accumulated in the medullary interstitial space, diffuses as lipid-soluble NH_3 into collecting duct urine and combines with secreted H^+ to form NH_4^+. The collecting duct epithelium is impermeable to the lipid-insoluble NH_4^+, so ammonia is trapped in an acidic urine and excreted as NH_4^+ (see Fig. 25.5). The intercalated cells of the collecting duct are involved in acid-base transport and are of two major types: an acid-secreting **α-intercalated cell** and a bicarbonate-secreting **β-intercalated cell**. The α-intercalated cell has a vacuolar type of H^+-ATPase (the same kind as is found in lysosomes, endosomes, and secretory vesicles) and an H^+/K^+-ATPase (similar to that found in stomach and colon epithelial cells) in the luminal plasma membrane and a Cl^-/HCO_3^- exchanger in the basolateral plasma membrane (Fig. 25.6). The β-intercalated cell has the opposite polarity.

A more acidic blood pH results in the insertion of cytoplasmic H^+ pumps into the luminal plasma membrane of α-intercalated cells and enhanced H^+ secretion. If the blood is made alkaline, HCO_3^- secretion by β-intercalated cells is increased. Because the amounts of HCO_3^- secreted are ordinarily small compared to the amounts filtered and reabsorbed, HCO_3^- secretion will not be included in the remaining discussion.

The Reabsorption of Filtered HCO_3^- Restores Lost HCO_3^- to the Blood

HCO_3^- is freely filtered at the glomerulus, about 4,320 mEq/day (180 L/day × 24 mEq/L). Urinary loss of even a small portion of this HCO_3^- would lead to acidic blood and impair the body's ability to buffer its daily load of metabolically produced H^+. The kidney tubules have the important task of recovering the filtered HCO_3^- and returning it to the blood.

Figure 25.7 shows how HCO_3^- filtration, reabsorption, and excretion normally vary with plasma $[HCO_3^-]$. This type of graph should be familiar (Fig. 23.8). The y-axis of the graph is unusual, however, because amounts of HCO_3^- per minute are factored by the GFR. The data are expressed in this way because the maximal rate of tubular reabsorption of HCO_3^- varies with GFR. The amount of HCO_3^- excreted in the urine per unit time is calculated as the difference between filtered and reabsorbed amounts. At low plasma concentrations of HCO_3^- (below about 26 mEq/L), all of the filtered HCO_3^- is reabsorbed. Because the plasma $[HCO_3^-]$ and pH were decreased by ingestion of an acid-

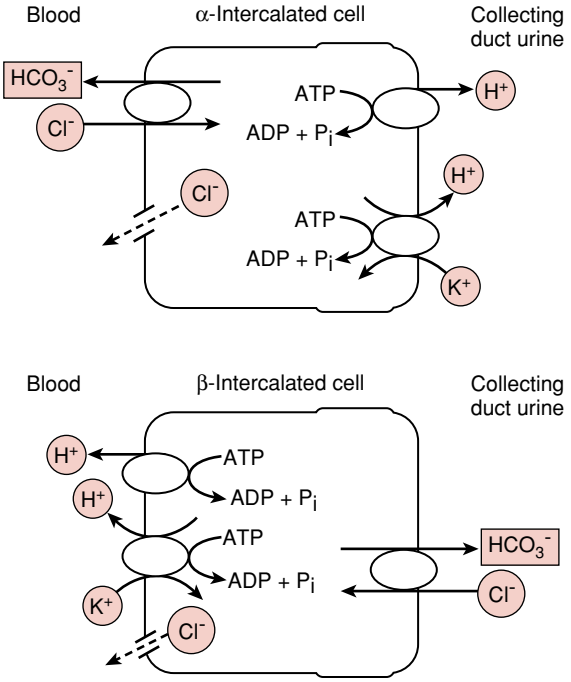

FIGURE 25.6 **Collecting duct intercalated cells.** The α-intercalated cell secretes H^+ via an electrogenic, vacuolar H^+-ATPase and electroneutral H^+/K^+-ATPase and adds HCO_3^- to the blood via a basolateral plasma membrane Cl^-/HCO_3^- exchanger. The β-intercalated cell, which is located in cortical collecting ducts, has the opposite polarity and secretes HCO_3^-.

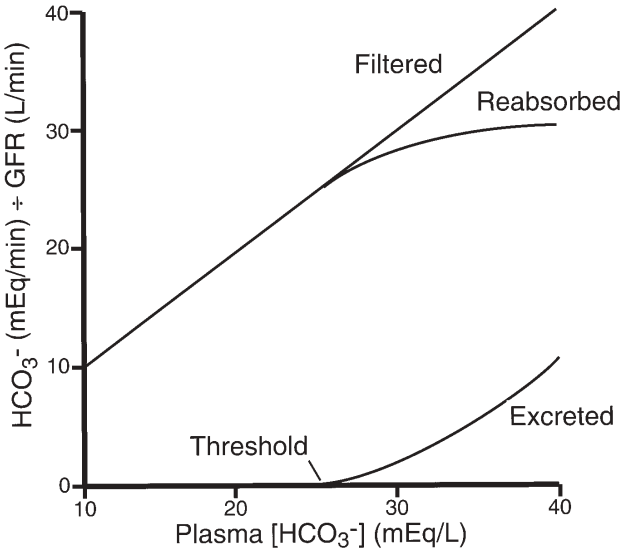

FIGURE 25.7 **The filtration, reabsorption, and excretion of HCO_3^-.** Decreases in plasma $[HCO_3^-]$ were produced by ingestion of NH_4Cl and increases were produced by intravenous infusion of a solution of $NaHCO_3$. All the filtered HCO_3^- was reabsorbed below a plasma concentration of about 26 mEq/L. Above this value ("threshold"), appreciable quantities of filtered HCO_3^- were excreted in the urine. (Adapted from Pitts RF, Ayer JL, Schiess WA. The renal regulation of acid-base balance in man. III. The reabsorption and excretion of bicarbonate. J Clin Invest 1949;28:35–44.)

ifying salt (NH_4Cl), it makes good sense that the kidneys conserve filtered HCO_3^- in this situation.

If the plasma $[HCO_3^-]$ is raised to high levels because of intravenous infusion of solutions containing $NaHCO_3$ for example, filtered HCO_3^- exceeds the reabsorptive capacity of the tubules and some HCO_3^- will be excreted in the urine (see Fig. 25.7). This also makes good sense. If the blood is too alkaline, the kidneys excrete HCO_3^-. This loss of base would return the pH of the blood to its normal value.

At the cellular level (see Fig. 25.8), filtered HCO_3^- is not reabsorbed directly across the tubule's luminal plasma membrane as, for example, is glucose. Instead, filtered HCO_3^- is reabsorbed indirectly via H^+ secretion in the following way. About 90% of the filtered HCO_3^- is reabsorbed in the proximal convoluted tubule, and we will emphasize events at this site. H^+ is secreted into the tubule lumen mainly via the Na^+/H^+ exchanger in the luminal membrane. It combines with filtered HCO_3^- to form H_2CO_3. Carbonic anhydrase (CA) in the luminal membrane (brush border) of the proximal tubule catalyzes the dehydration of H_2CO_3 to CO_2 and water in the lumen. The CO_2 diffuses back into the cell.

Inside the cell, the hydration of CO_2 (catalyzed by intracellular CA) yields H_2CO_3, which instantaneously forms H^+ and HCO_3^-. The H^+ is secreted into the lumen, and the HCO_3^- ion moves into the blood surrounding the tubules. In proximal tubule cells, this movement is favored by the inside negative membrane potential of the cell and by an electrogenic cotransporter in the basolateral membrane that simultaneously transports three HCO_3^- and one Na^+.

The reabsorption of filtered HCO_3^- does not result in H^+ excretion or the formation of any "new" HCO_3^-. The secreted H^+ is not excreted because it combines with filtered HCO_3^- that is, indirectly, reabsorbed. There is no net addition of HCO_3^- to the body in this operation. It is simply a recovery or reclamation process.

Excretion of Titratable Acid and Ammonia Generates New Bicarbonate

When H^+ is excreted as titratable acid and ammonia, new HCO_3^- is formed and added to the blood. New HCO_3^- replaces the HCO_3^- used to buffer the strong acids produced by metabolism.

The formation of new HCO_3^- and the excretion of H^+ are like two sides of the same coin. This fact is apparent if we assume that H_2CO_3 is the source of H^+:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \begin{matrix} \nearrow\ H^+\ \text{(urine)} \\ \searrow\ HCO_3^-\ \text{(blood)} \end{matrix} \qquad (23)$$

A loss of H^+ in the urine is equivalent to adding new HCO_3^- to the blood. The same is true if H^+ is lost from the body via another route, such as by vomiting of acidic gastric juice. This process leads to a rise in plasma $[HCO_3^-]$. *Conversely, a loss of HCO_3^- from the body is equivalent to adding H^+ to the blood.*

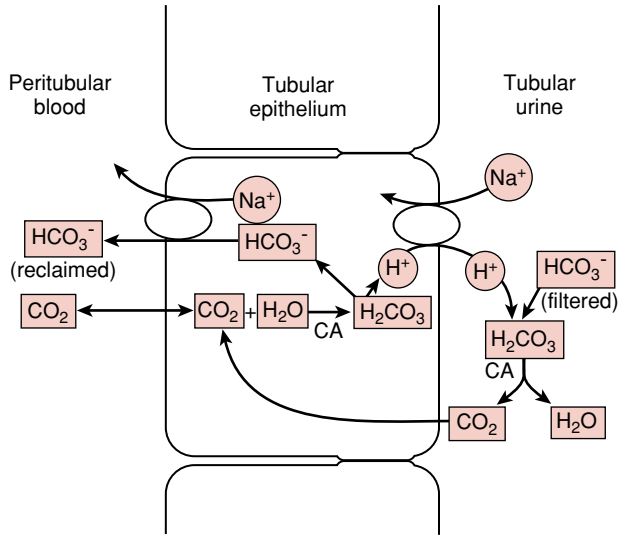

FIGURE 25.8 **A cell model for HCO_3^- reabsorption.** Filtered HCO_3^- combines with secreted H^+ and is reabsorbed indirectly. Carbonic anhydrase (CA) is present in the cells and in the proximal tubule on the brush border.

Titratable Acid Excretion. Figure 25.9 shows a cell model for the formation of titratable acid. In this figure, $H_2PO_4^-$ is the titratable acid formed. H^+ and HCO_3^- are produced in the cell from H_2CO_3. The secreted H^+ combines with the basic form of the phosphate (HPO_4^{2-}) to form the acid phosphate ($H_2PO_4^-$). The secreted H^+ replaces one of the Na^+ ions accompanying the basic phosphate. The new HCO_3^- generated in the cell moves into the blood, together with Na^+. For each mEq of H^+ excreted in the urine as titratable acid, a mEq of new HCO_3^- is added to the blood. This process eliminates H^+ in the urine, replaces ECF HCO_3^-, and restores a normal blood pH.

The amount of titratable acid excreted depends on two factors: the pH of the urine and the availability of buffer. If the urine pH is lowered, more titratable acid can form. The supply of phosphate and other buffers is usually limited. To excrete large amounts of acid, the kidneys must rely on increased ammonia excretion.

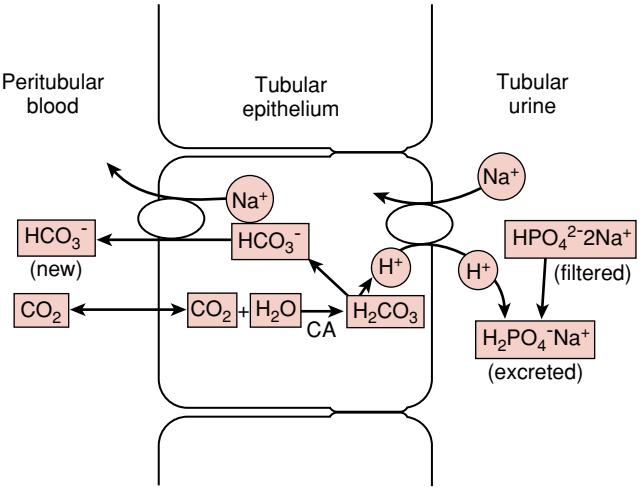

FIGURE 25.9 **A cell model for the formation of titratable acid.** Titratable acid (e.g., $H_2PO_4^-$) is formed when secreted H^+ is bound to a buffer base (e.g., HPO_4^{2-}) in the tubular urine. For each mEq of titratable acid excreted, a mEq of new HCO_3^- is added to the peritubular capillary blood.

Ammonia Excretion. Figure 25.10 shows a cell model for the excretion of ammonia. Most ammonia is synthesized in proximal tubule cells by deamidation and deamination of the amino acid glutamine:

$$\text{Glutamine} \xrightarrow[\text{Glutaminase}]{} \text{Glutamate}^- \xrightarrow[\text{Glutamate dehydrogenase}]{} \alpha\text{-Ketoglutarate}^{2-} \quad (24)$$

with NH_4^+ released at each step.

As discussed earlier, ammonia is secreted into the urine by two mechanisms. As NH_3, it diffuses into the tubular urine; as NH_4^+, it substitutes for H^+ on the Na^+/H^+ exchanger. In the lumen, NH_3 combines with secreted H^+ to form NH_4^+, which is excreted.

For each mEq of H^+ excreted as NH_4^+, one mEq of new HCO_3^- is added to the blood. The hydration of CO_2 in the tubule cell produces H^+ and HCO_3^-, as described earlier. Two H^+s are consumed when the anion α-ketoglutarate^{2-} is converted into CO_2 and water or into glucose in the cell. The new HCO_3^- returns to the blood along with Na^+.

If excess acid is added to the body, urinary ammonia excretion is increased for two reasons. First, a more acidic urine traps more ammonia (as NH_4^+) in the urine. Second, renal ammonia synthesis from glutamine increases over sev-

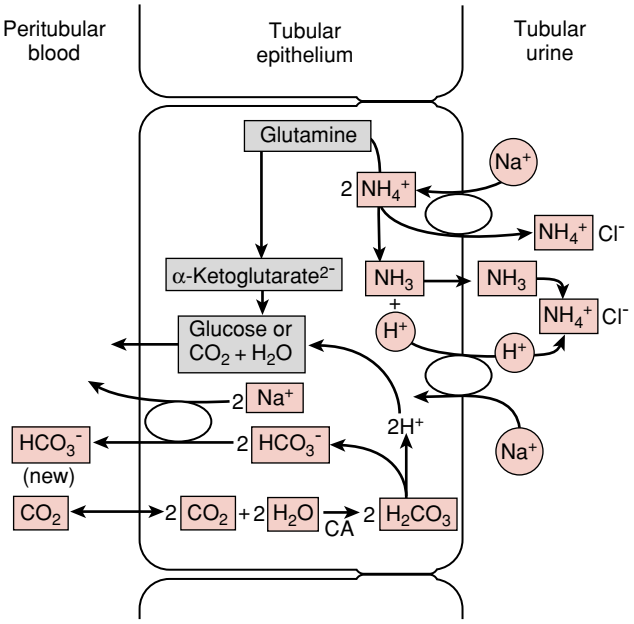

FIGURE 25.10 **A cell model for renal synthesis and excretion of ammonia.** Ammonium ions are formed from glutamine in the cell and are secreted into the tubular urine (top). H^+ from H_2CO_3 (bottom) is consumed when α-ketoglutarate is converted into glucose or CO_2 and H_2O. New HCO_3^- is added to the peritubular capillary blood—1 mEq for each mEq of NH_4^+ excreted in the urine.

eral days. Enhanced renal ammonia synthesis and excretion is a lifesaving adaptation because it allows the kidneys to remove large H^+ excesses and add more new HCO_3^- to the blood. Also, the excreted NH_4^+ can substitute in the urine for Na^+ and K^+, diminishing the loss of these cations. With severe metabolic acidosis, ammonia excretion may increase almost 10-fold.

Several Factors Influence Renal Excretion of Hydrogen Ions

Several factors influence the renal excretion of H^+, including intracellular pH, arterial blood P_{CO_2}, carbonic anhydrase activity, Na^+ reabsorption, plasma $[K^+]$, and aldosterone (Fig. 25.11).

Intracellular pH. The pH in kidney tubule cells is a key factor influencing the secretion and, therefore, the excretion of H^+. A fall in pH (increased $[H^+]$) enhances H^+ secretion. A rise in pH (decreased $[H^+]$) lowers H^+ secretion.

Arterial Blood P_{CO_2}. An increase in P_{CO_2} increases the formation of H^+ from H_2CO_3, leading to enhanced renal H^+ secretion and excretion—a useful compensation for any condition in which the blood contains too much H_2CO_3. (This will be discussed later, when we consider respiratory acidosis.) A decrease in P_{CO_2} results in lowered H^+ secretion and, consequently, less complete reabsorption of filtered HCO_3^- and a loss of base in the urine (a useful compensation for respiratory alkalosis, also discussed later).

Carbonic Anhydrase Activity. The enzyme carbonic anhydrase catalyzes two key reactions in urinary acidification:

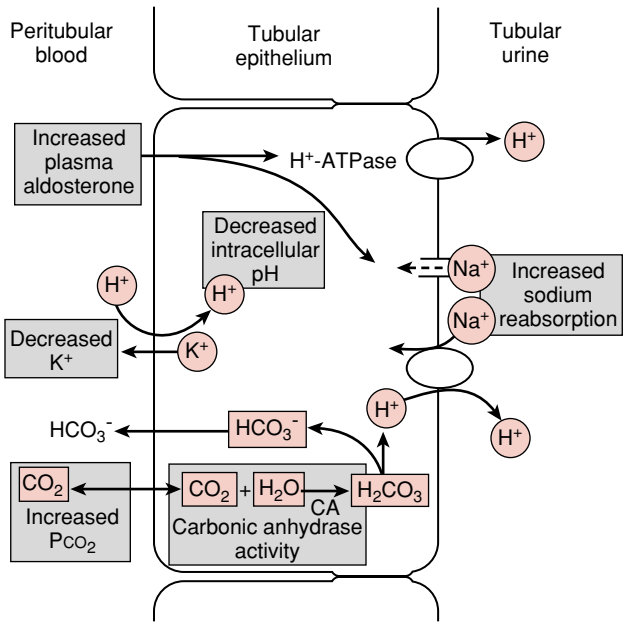

FIGURE 25.11 Factors leading to increased H^+ secretion by the kidney tubule epithelium. (See text for details.)

1) Hydration of CO_2 in the cells, forming H_2CO_3 and yielding H^+ for secretion

2) Dehydration of H_2CO_3 to H_2O and CO_2 in the proximal tubule lumen, an important step in the reabsorption of filtered HCO_3^-

If carbonic anhydrase is inhibited (usually by a drug), large amounts of filtered HCO_3^- may escape reabsorption. This situation leads to a fall in blood pH.

Sodium Reabsorption. Na^+ reabsorption is closely linked to H^+ secretion. In the proximal tubule, the two ions are directly linked, both being transported by the Na^+/H^+ exchanger in the luminal plasma membrane. The relation is less direct in the collecting ducts. Enhanced Na^+ reabsorption in the ducts leads to a more negative intraluminal electrical potential, which favors H^+ secretion by its electrogenic H^+-ATPase. The avid renal reabsorption of Na^+ observed in states of volume depletion is accompanied by a parallel rise in urinary H^+ excretion.

Plasma Potassium Concentration. Changes in plasma $[K^+]$ influence the renal excretion of H^+. A fall in plasma $[K^+]$ favors the movement of K^+ from body cells into interstitial fluid (or blood plasma) and a reciprocal movement of H^+ into cells. In the kidney tubule cells, these movements lower intracellular pH and increase H^+ secretion. K^+ depletion also stimulates ammonia synthesis by the kidneys. The result is the complete reabsorption of filtered HCO_3^- and the enhanced generation of new HCO_3^- as more titratable acid and ammonia are excreted. Consequently, hypokalemia (or a decrease in body K^+ stores) leads to increased plasma $[HCO_3^-]$ (metabolic alkalosis). Hyperkalemia (or excess K^+ in the body) results in the opposite changes: an increase in intracellular pH, decreased H^+ secretion, incomplete reabsorption of filtered HCO_3^-, and a fall in plasma $[HCO_3^-]$ (metabolic acidosis).

Aldosterone. Aldosterone stimulates the collecting ducts to secrete H^+ by three actions:

1) It directly stimulates the H^+-ATPase in collecting duct α-intercalated cells.

2) It enhances collecting duct Na^+ reabsorption, which leads to a more negative intraluminal potential and, consequently, promotes H^+ secretion by the electrogenic H^+-ATPase.

3) It promotes K^+ secretion. This response leads to hypokalemia, which increases renal H^+ secretion.

Hyperaldosteronism results in enhanced renal H^+ excretion and an alkaline blood pH; the opposite occurs with hypoaldosteronism.

pH gradient. The secretion of H^+ by the kidney tubules and collecting ducts is gradient-limited. The collecting ducts cannot lower the urine pH below 4.5, corresponding to a urine/plasma $[H^+]$ gradient of $10^{-4.5}/10^{-7.4}$ or 800/1 when the plasma pH is 7.4. If more buffer base (NH_3, HPO_4^{2-}) is available in the urine, more H^+ can be secreted before the limiting gradient is reached. In some kidney tubule disorders, the secretion of H^+ is gradient-limited (see Clinical Focus Box 25.1).

CLINICAL FOCUS BOX 25.1

Renal Tubular Acidosis

Renal tubular acidosis (RTA) is a group of kidney disorders characterized by chronic metabolic acidosis, a normal plasma anion gap, and the absence of renal failure. The kidneys show inadequate H^+ secretion by the distal nephron, excessive excretion of HCO_3^-, or reduced excretion of NH_4^+.

In classic **type 1 (distal) RTA**, the ability of the collecting ducts to lower urine pH is impaired. This condition can be caused by inadequate secretion of H^+ (defective H^+-ATPase or H^+/K^+-ATPase) or abnormal leakiness of the collecting duct epithelium so that secreted H^+ ions diffuse back from lumen to blood. Because the urine pH is inappropriately high, titratable acid excretion is diminished and trapping of ammonia in the urine (as NH_4^+) is decreased. Type 1 RTA may be the result of an inherited defect, autoimmune disease, treatment with lithium or the antibiotic amphotericin B, or the result of diseases of the kidney medulla. A diagnosis of this form of RTA is established by challenging the subject with a standard oral dose of NH_4Cl and measuring the urine pH for the next several hours. This results in a urine pH below 5.0 in healthy people. In subjects with type 1 RTA, however, urine pH will not decrease below 5.5. Treatment of type 1 RTA involves daily administration of modest amounts of alkali (HCO_3^-, citrate) sufficient to cover daily metabolic acid production.

In **type 2 (proximal) RTA**, HCO_3^- reabsorption by the proximal tubule is impaired, leading to excessive losses of HCO_3^- in the urine. As a consequence, the plasma $[HCO_3^-]$ falls and chronic metabolic acidosis ensues. In the new steady state, the tubules are able to reabsorb the filtered HCO_3^- load more completely because the filtered load is reduced. The distal nephron is no longer overwhelmed by HCO_3^- and the urine pH is acidic. In type 2 RTA, the administration of an NH_4Cl challenge results in a urine pH below 5.5. This disorder may be inherited, may be associated with several acquired conditions that result in a generalized disorder of proximal tubule transport, or may result from the inhibition of proximal tubule carbonic anhydrase by drugs such as acetazolamide. Treatment requires the daily administration of large amounts of alkali because when the plasma $[HCO_3^-]$ is raised, excessive urinary excretion of filtered HCO_3^- occurs.

Type 4 RTA (there is no type 3 RTA) is also known as **hyperkalemic distal RTA**. Collecting duct secretion of both K^+ and H^+ is reduced, explaining the hyperkalemia and metabolic acidosis. Hyperkalemia reduces renal ammonia synthesis, resulting in reduced net acid excretion and a fall in plasma $[HCO_3^-]$. The urine pH can go below 5.5 after an NH_4Cl challenge because there is little ammonia in the urine to buffer secreted H^+. The underlying disorder is a result of inadequate production of aldosterone or impaired aldosterone action. Treatment of type 4 RTA requires lowering the plasma $[K^+]$ to normal; if this therapy is successful, alkali may not be needed.

REGULATION OF INTRACELLULAR PH

The intracellular and extracellular fluids are linked by exchanges across plasma membranes of H^+, HCO_3^-, various acids and bases, and CO_2. By stabilizing ECF pH, the body helps to protect intracellular pH.

If H^+ ions were passively distributed across plasma membranes, intracellular pH would be lower than what is seen in most body cells. In skeletal muscle cells, for example, we can calculate from the Nernst equation (see Chapter 2) and a membrane potential of −90 mV that cytosolic pH should be 5.9 if ECF pH is 7.4; actual measurements, however, indicate a pH of 6.9. From this discrepancy, two conclusions are clear: H^+ ions are not at equilibrium across the plasma membrane, and the cell must use active mechanisms to extrude H^+.

Cells are typically threatened by acidic metabolic endproducts and by the tendency for H^+ to diffuse into the cell down the electrical gradient (Fig. 25.12). H^+ is extruded by Na^+/H^+ exchangers, which are present in nearly all body cells. Five different isoforms of these exchangers (designated NHE1, NHE2, etc.), with different tissue distributions, have been identified. These transporters exchange one H^+ for one Na^+ and, therefore, function in an electrically neutral fashion. Active extrusion of H^+ keeps the internal pH within narrow limits.

The activity of the Na^+/H^+ exchanger is regulated by intracellular pH and a variety of hormones and growth factors (Fig. 25.13). Not surprisingly, an increase in intracellu-

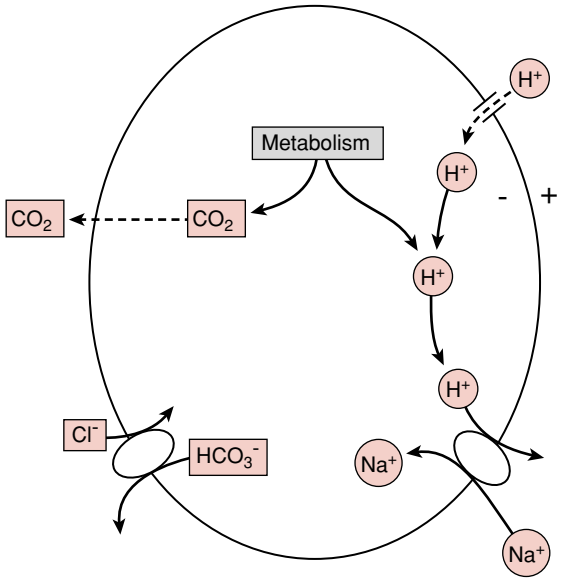

FIGURE 25.12 **Cell acid-base balance.** Body cells usually maintain a constant intracellular pH. The cell is acidified by the production of H^+ from metabolism and the influx of H^+ from the ECF (favored by the inside negative plasma membrane potential). To maintain a stable intracellular pH, the cell must extrude hydrogen ions at a rate matching their input. Many cells also possess various HCO_3^- transporters (not depicted), which defend against excess acid or base.

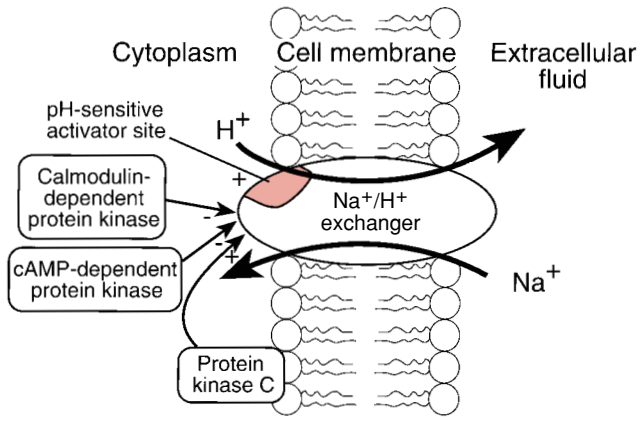

FIGURE 25.13 **The plasma membrane Na^+/H^+ exchanger.** This exchanger plays a key role in regulating intracellular pH in most body cells and is activated by a decrease in cytoplasmic pH. Many hormones and growth factors, acting via intracellular second messengers and protein kinases, can increase (+) or decrease (−) the activity of the exchange.

lar $[H^+]$ stimulates the exchanger but not only because of more substrate (H^+) for the exchanger. H^+ also stimulates the exchanger by protonating an activator site on the cytoplasmic side of the exchanger, making the exchanger more effective in dealing with the threat of intracellular acidosis. Many hormones and growth factors, via intracellular second messengers, activate various protein kinases that stimulate or inhibit the Na^+/H^+ exchanger. In this way, they produce changes in intracellular pH, which may lead to changes in cell activity.

Besides extruding H^+, the cell can deal with acids and bases in other ways. In some cells, various HCO_3^- transporting systems (e.g., Na^+-dependent and Na^+-independent Cl^-/HCO_3^- exchangers) may be present in plasma membranes. These exchangers may be activated by changes in intracellular pH. Cells have large stores of protein and organic phosphate buffers, which can bind or release H^+. Various chemical reactions in cells can also use up or release H^+. For example, the conversion of lactic acid to CO_2 and water to glucose effectively disposes of acid. In addition, various cell organelles may sequester H^+. For example, H^+-ATPase in endosomes and lysosomes pumps H^+ out of the cytosol into these organelles. In summary, ion transport, buffering mechanisms, and metabolic reactions all ensure a relatively stable intracellular pH.

DISTURBANCES OF ACID-BASE BALANCE

Table 25.2 lists the normal values for the pH (or $[H^+]$), P_{CO_2}, and $[HCO_3^-]$ of arterial blood plasma. A blood pH of less than 7.35 ($[H^+] > 45$ nmol/L) indicates **acidemia**. A blood pH above 7.45 ($[H^+] < 35$ nmol/L) indicates **alkalemia**. The range of pH values compatible with life is approximately 6.8 to 7.8 ($[H^+] = 160$ to 16 nmol/L).

Four **simple acid-base disturbances** may lead to an abnormal blood pH: respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis. The word "simple" indicates a single primary cause for the disturbance. **Acidosis** is an abnormal process that tends to produce acidemia. **Alkalosis** is an abnormal process that tends to produce alkalemia. If there is too much or too little CO_2, a **respiratory disturbance** is present. If the problem is too much or too little HCO_3^-, a **metabolic** (or **nonrespiratory**) **disturbance** of acid-base balance is present. Table 25.3 summarizes the changes in blood pH (or $[H^+]$), plasma $[HCO_3^-]$, and P_{CO_2} that occur in each of the four simple acid-base disturbances.

TABLE 25.2 **Normal Arterial Blood Plasma Acid-Base Values**

	Mean	Range[a]
pH	7.40	7.35–7.45
$[H^+]$, nmol/L	40	45–35
P_{CO_2}, mm Hg	40	35–45
$[HCO_3^-]$, mEq/L	24	22–26

[a] The range extends from 2 standard deviations below to 2 standard deviations above the mean and encompasses 95% of the healthy population.

In considering acid-base disturbances, it is helpful to recall the Henderson-Hasselbalch equation for HCO_3^-/CO_2:

$$pH = 6.10 + \log \frac{[HCO_3^-]}{0.03\ P_{CO_2}} \qquad (25)$$

If the primary problem is a change in $[HCO_3^-]$ or P_{CO_2}, the pH can be brought closer to normal by changing the other member of the buffer pair *in the same direction*. For example, if P_{CO_2} is primarily decreased, a decrease in plasma $[HCO_3^-]$ will minimize the change in pH. In various acid-base disturbances, the lungs adjust the blood P_{CO_2} and the kidneys adjust the plasma $[HCO_3^-]$ to reduce departures of pH from normal; these adjustments are called **compensations** (Table 25.4). Compensations generally do not bring about normal blood pH.

Respiratory Acidosis Results From an Accumulation of Carbon Dioxide

Respiratory acidosis is an abnormal process characterized by CO_2 accumulation. The CO_2 build-up pushes the following reactions to the right:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \qquad (26)$$

Blood $[H_2CO_3]$ increases, leading to an increase in $[H^+]$ or a fall in pH. Respiratory acidosis is usually caused by a failure to expire metabolically produced CO_2 at an adequate rate, leading to accumulation of CO_2 in the blood and a fall in blood pH. This disturbance may be a result of a decrease in overall alveolar ventilation (hypoventilation) or, as occurs commonly in lung disease, a mismatch between ventilation and perfusion. Respiratory acidosis also occurs if a person breathes CO_2-enriched air.

Chemical Buffering. In respiratory acidosis, more than 95% of the chemical buffering occurs within cells. The cells

TABLE 25.3 Directional Changes in Arterial Blood Plasma Values in the Four Simple Acid-Base Disturbances[a]

	Arterial Plasma				
Disturbance	pH	$[H^+]$	$[HCO_3^-]$	P_{CO_2}	Compensatory Response
Respiratory acidosis	↓	↑	↑	⇑	Kidneys increase H^+ excretion
Respiratory alkalosis	↑	↓	↓	⇓	Kidneys increase HCO_3^- excretion
Metabolic acidosis	↓	↑	⇓	↓	Alveolar hyperventilation; kidneys increase H^+ excretion
Metabolic alkalosis	↑	↓	⇑	↑	Alveolar hypoventilation; kidneys increase HCO_3^- excretion

[a] Heavy arrows indicate the main effect.

contain many proteins and organic phosphates that can bind H^+. For example, hemoglobin (Hb) in red blood cells combines with H^+ from H_2CO_3, minimizing the increase in free H^+. Recall from Chapter 21 the buffering reaction:

$$H_2CO_3 + HbO_2^- \rightleftharpoons HHb + O_2 + HCO_3^- \quad (27)$$

This reaction raises the plasma $[HCO_3^-]$. In *acute* respiratory acidosis, such chemical buffering processes in the body lead to an increase in plasma $[HCO_3^-]$ of about 1 mEq/L for each 10 mm Hg increase in P_{CO_2} (see Table 25.4). Bicarbonate is not a buffer for H_2CO_3 because the reaction

$$H_2CO_3 + HCO_3^- \rightleftharpoons HCO_3^- + H_2CO_3 \quad (28)$$

is simply an exchange reaction and does not affect the pH.

An example illustrates how chemical buffering reduces a fall in pH during respiratory acidosis. Suppose P_{CO_2} increased from a normal value of 40 mm Hg to 70 mm Hg ($[CO_{2(d)}] = 2.1$ mmol/L). If there were no body buffer bases that could accept H^+ from H_2CO_3 (i.e., if there was no measurable increase in $[HCO_3^-]$), the resulting pH would be 7.16:

$$pH = 6.10 + \log \frac{[24]}{[2.1]} = 7.16 \quad (29)$$

In acute respiratory acidosis, a 3 mEq/L increase in plasma $[HCO_3^-]$ occurs with a 30 mm Hg rise in P_{CO_2} (see Table 25.4). Therefore, the pH is 7.21:

$$pH = 6.10 + \log \frac{[24 + 3]}{[2.1]} = 7.21 \quad (30)$$

The pH of 7.21 is closer to a normal pH because body buffer bases (mainly intracellular buffers) such as proteins and phosphates combined with H^+ ions liberated from H_2CO_3.

Respiratory Compensation. Respiratory acidosis produces a rise in P_{CO_2} and a fall in pH and is often associated with hypoxia. These changes stimulate breathing (see Chapter 22) and diminish the severity of the acidosis. In other words, a person would be worse off if the respiratory system did not reflexively respond to the abnormalities in blood P_{CO_2}, pH, and P_{O_2}.

Renal Compensation. The kidneys compensate for respiratory acidosis by adding more H^+ to the urine and adding new HCO_3^- to the blood. The increased P_{CO_2} stimulates renal H^+ secretion, which allows the reabsorption of all filtered HCO_3^-. Excess H^+ is excreted as titratable acid and NH_4^+; these processes add new HCO_3^- to the blood, causing plasma $[HCO_3^-]$ to rise. This compensation takes several days to fully develop.

With *chronic* respiratory acidosis, plasma $[HCO_3^-]$ increases, on average, by 4 mEq/L for each 10 mm Hg rise in P_{CO_2} (see Table 25.4). This rise exceeds that seen with acute respiratory acidosis because of the renal addition of HCO_3^- to the blood. One would expect a person with chronic respiratory acidosis and a P_{CO_2} of 70 mm Hg to have an increase in plasma HCO_3^- of 12 mEq/L. The blood pH would be 7.33:

$$pH = 6.10 + \log \frac{[24 + 12]}{[2.1]} = 7.33 \quad (31)$$

TABLE 25.4 Compensatory Responses in Acid-Base Disturbances[a]

Respiratory acidosis	
Acute	1 mEq/L increase in plasma $[HCO_3^-]$ for each 10 mm Hg increase in P_{CO_2}[b]
Chronic	4 mEq/L increase in plasma $[HCO_3^-]$ for each 10 mm Hg increase in P_{CO_2}[c]
Respiratory alkalosis	
Acute	2 mEq/L decrease in plasma $[HCO_3^-]$ for each 10 mm Hg decrease in P_{CO_2}[d]
Chronic	4 mEq/L decrease in plasma $[HCO_3^-]$ for each 10 mm Hg decrease in P_{CO_2}[d]
Metabolic acidosis	1.3 mm Hg decrease in P_{CO_2} for each 1 mEq/L decrease in plasma $[HCO_3^-]$[d]
Metabolic alkalosis	0.7 mm Hg increase in P_{CO_2} for each 1 mEq/L increase in plasma $[HCO_3^-]$[d]

From Valtin H, Gennari FJ. Acid-Base Disorders. Basic Concepts and Clinical Management. Boston: Little, Brown, 1987.

[a] Empirically determined average changes measured in people with simple acid-base disorders.

[b] This change is primarily a result of chemical buffering.

[c] This change is primarily a result of renal compensation.

[d] This change is a result of respiratory compensation.

With chronic respiratory acidosis, time for renal compensation is allowed, so blood pH (in this example, 7.33) is much closer to normal than is observed during acute respiratory acidosis (pH 7.21).

Respiratory Alkalosis Results From an Excessive Loss of Carbon Dioxide

Respiratory alkalosis is most easily understood as the opposite of respiratory acidosis; it is an abnormal process causing the loss of too much CO_2. This loss causes blood $[H_2CO_3]$ and, thus, $[H^+]$ to fall (pH rises). Alveolar hyperventilation causes respiratory alkalosis. Metabolically produced CO_2 is flushed out of the alveolar spaces more rapidly than it is added by the pulmonary capillary blood. This situation causes alveolar and arterial P_{CO_2} to fall. Hyperventilation and respiratory alkalosis can be caused by voluntary effort, anxiety, direct stimulation of the medullary respiratory center by some abnormality (e.g., meningitis, fever, aspirin intoxication), or hypoxia caused by severe anemia or high altitude.

Chemical Buffering. As with respiratory acidosis, during respiratory alkalosis more than 95% of chemical buffering occurs within cells. Cell proteins and organic phosphates liberate H^+ ions, which are added to the ECF and lower the plasma $[HCO_3^-]$, reducing the alkaline shift in pH.

With *acute* respiratory alkalosis, plasma $[HCO_3^-]$ falls by about 2 mEq/L for each 10 mm Hg drop in P_{CO_2} (see Table 25.4). For example, if P_{CO_2} drops from 40 to 20 mm Hg ($[CO_{2(d)}] = 0.6$ mmol/L) plasma $[HCO_3^-]$ falls by 4 mEq/L, and the pH will be 7.62:

$$pH = 6.10 + \log \frac{[24 - 4]}{[0.6]} = 7.62 \qquad (32)$$

If plasma $[HCO_3^-]$ had not changed, the pH would have been 7.70:

$$pH = 6.10 + \log \frac{[24]}{[0.6]} = 7.70 \qquad (33)$$

Respiratory Compensation. Although hyperventilation causes respiratory alkalosis, hyperventilation also causes changes (a fall in P_{CO_2} and a rise in blood pH) that inhibit ventilation and, therefore, limit the extent of hyperventilation.

Renal Compensation. The kidneys compensate for respiratory alkalosis by excreting HCO_3^- in the urine, thereby, getting rid of base. A reduced P_{CO_2} reduces H^+ secretion by the kidney tubule epithelium. As a result, some of the filtered HCO_3^- is not reabsorbed. When the urine becomes more alkaline, titratable acid excretion vanishes and little ammonia is excreted. The enhanced output of HCO_3^- causes plasma $[HCO_3^-]$ to fall.

Chronic respiratory alkalosis is accompanied by a 4 mEq/L fall in plasma $[HCO_3^-]$ for each 10 mm Hg drop in P_{CO_2} (see Table 25.4). For example, in a person with chronic hyperventilation and a P_{CO_2} of 20 mm Hg, the blood pH is

$$pH = 6.10 + \log \frac{[24 - 8]}{[0.6]} = 7.53 \qquad (34)$$

This pH is closer to normal than the pH of 7.62 of acute respiratory alkalosis. The difference between the two situations is largely a result of renal compensation.

Metabolic Acidosis Results From a Gain of Noncarbonic Acid or a Loss of Bicarbonate

Metabolic acidosis is an abnormal process characterized by a gain of acid (other than H_2CO_3) or a loss of HCO_3^-. Either causes plasma $[HCO_3^-]$ and pH to fall. If a strong acid is added to the body, the reactions

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2 \qquad (35)$$

are pushed to the right. The added H^+ consumes HCO_3^-. If a lot of acid is infused rapidly, P_{CO_2} rises, as the equation predicts. This increase occurs only transiently, however, because the body is an open system, and the lungs expire CO_2 as it is generated. P_{CO_2} actually falls below normal because an acidic blood pH stimulates ventilation (see Fig. 25.3).

Many conditions can produce metabolic acidosis, including renal failure, uncontrolled diabetes mellitus, lactic acidosis, the ingestion of acidifying agents such as NH_4Cl, abnormal renal excretion of HCO_3^-, and diarrhea. In renal failure, the kidneys cannot excrete H^+ fast enough to keep up with metabolic acid production and, in uncontrolled diabetes mellitus, the production of ketone body acids increases. Lactic acidosis results from tissue hypoxia. Ingested NH_4Cl is converted into urea and a strong acid, HCl, in the liver. Diarrhea causes a loss of alkaline intestinal fluids. Clinical Focus Box 25.2 discusses the metabolic acidosis seen in uncontrolled diabetes mellitus.

Chemical Buffering. Excess acid is chemically buffered in extracellular and intracellular fluids and bone. In metabolic acidosis, roughly half the buffering occurs in cells and bone. HCO_3^- is the principal buffer in the ECF.

Respiratory Compensation. The acidic blood pH stimulates the respiratory system to lower blood P_{CO_2}. This action lowers blood $[H_2CO_3]$ and tends to alkalinize the blood, opposing the acidic shift in pH. Metabolic acidosis is accompanied on average by a 1.3 mm Hg fall in P_{CO_2} for each 1 mEq/L drop in plasma $[HCO_3^-]$ (see Table 25.4). Suppose, for example, the infusion of a strong acid causes the plasma $[HCO_3^-]$ to drop from 24 to 12 mEq/L. If there was no respiratory compensation and the P_{CO_2} did not change from its normal value of 40 mm Hg, the pH would be 7.10:

$$pH = 6.10 + \log \frac{[12]}{[1.2]} = 7.10 \qquad (36)$$

CLINICAL FOCUS BOX 25.2

Metabolic Acidosis in Diabetes Mellitus

Diabetes mellitus is a common disorder characterized by an insufficient secretion of insulin or insulin-resistance by the major target tissues (skeletal muscle, liver, and adipocytes). A severe **metabolic acidosis** may develop in uncontrolled diabetes mellitus.

Acidosis occurs because insulin deficiency leads to decreased glucose utilization, a diversion of metabolism toward the utilization of fatty acids, and an overproduction of ketone body acids (acetoacetic acid and β-hydroxybutyric acids). Ketone body acids are fairly strong acids (pK_a 4 to 5); they are neutralized in the body by HCO_3^- and other buffers. Increased production of these acids leads to a fall in plasma [HCO_3^-], an increase in plasma anion gap, and a fall in blood pH (acidemia).

Severe acidemia, whatever its cause, has many adverse effects on the body. It impairs myocardial contractility, resulting in a decrease in cardiac output. It causes arteriolar dilation, which leads to a fall in arterial blood pressure. Hepatic and renal blood flows are decreased. Reentrant arrhythmias and a decreased threshold for ventricular fibrillation can occur. The respiratory muscles show decreased strength and fatigue easily. Metabolic demands are increased due, in part, to activation of the sympathetic nervous system, but at the same time anaerobic glycolysis and ATP synthesis are reduced by acidemia. Hyperkalemia is favored and protein catabolism is enhanced. Severe acidemia causes impaired brain metabolism and cell volume regulation, leading to progressive obtundation and coma.

An increased acidity of the blood stimulates pulmonary ventilation, resulting in a compensatory lowering of alveolar and arterial blood P_{CO_2}. The consequent reduction in blood [H_2CO_3] acts to move the blood pH back toward normal. The labored, deep breathing that accompanies severe uncontrolled diabetes is called **Kussmaul's respiration**.

The kidneys compensate for metabolic acidosis by reabsorbing all the filtered HCO_3^-. They also increase the excretion of titratable acid, part of which is comprised of ketone body acids. But these acids can only be partially titrated to their acid form in the urine because the urine pH cannot go below 4.5. Therefore, ketone body acids are excreted mostly in their anionic form; because of the requirement of electroneutrality in solutions, increased urinary excretion of Na^+ and K^+ results.

An important compensation for the acidosis is increased renal synthesis and excretion of ammonia. This adaptive response takes several days to fully develop, but it allows the kidneys to dispose of large amounts of H^+ in the form NH_4^+. The NH_4^+ in the urine can replace Na^+ and K^+ ions, resulting in conservation of these valuable cations.

The severe acidemia, electrolyte disturbances, and volume depletion that accompany uncontrolled diabetes mellitus may be fatal. Addressing the underlying cause, rather than just treating the symptoms best achieves correction of the acid-base disturbance. Therefore, the administration of a suitable dose of insulin is usually the key element of therapy. In some patients with marked acidemia (pH < 7.10), $NaHCO_3$ solutions may be infused intravenously to speed recovery, but this does not correct the underlying metabolic problem. Losses of Na^+, K^+, and water should be replaced.

With respiratory compensation, the P_{CO_2} falls by 16 mm Hg (12 × 1.3) to 24 mm Hg ([$CO_{2(d)}$] = 0.72 mmol/L) and pH is 7.32:

$$pH = 6.10 + \log \frac{[12]}{[0.72]} = 7.32 \qquad (37)$$

This value is closer to normal than a pH of 7.10. The respiratory response develops promptly (within minutes) and is maximal after 12 to 24 hours.

Renal Compensation. The kidneys respond to metabolic acidosis by adding more H^+ to the urine. Since the plasma [HCO_3^-] is primarily lowered, the filtered load of HCO_3^- drops, and the kidneys can accomplish the complete reabsorption of filtered HCO_3^- (see Fig. 25.7). More H^+ is excreted as titratable acid and NH_4^+. With chronic metabolic acidosis, the kidneys make more ammonia. The kidneys can, therefore, add more new HCO_3^- to the blood, to replace lost HCO_3^-. If the underlying cause of metabolic acidosis is corrected, then healthy kidneys can correct the blood pH in a few days.

The Plasma Anion Gap Is Calculated From Na^+, Cl^-, and HCO_3^- Concentrations

The anion gap is a useful concept, especially when trying to determine the possible cause of a metabolic acidosis. In any body fluid, the sums of the cations and anions are equal because solutions are electrically neutral. For blood plasma, we can write

$$\Sigma \text{ cations} = \Sigma \text{ anions} \qquad (38)$$

or

$$[Na^+] + [\text{unmeasured cations}] = [Cl^-] + [HCO_3^-] + [\text{unmeasured anions}] \qquad (39)$$

The unmeasured cations include K^+, Ca^{2+}, and Mg^{2+} ions and, because these are present at relatively low concentrations (compared to Na^+) and are usually fairly constant, we choose to neglect them. The unmeasured anions include plasma proteins, sulfate, phosphate, citrate, lactate, and other organic anions. If we rearrange the above equation, we get

$$[\text{unmeasured anions}] \text{ or anion gap} = [Na^+] - [Cl^-] - [HCO_3^-] \qquad (40)$$

In a healthy person, the anion gap falls in the range of 8 to 14 mEq/L. For example, if plasma $[Na^+]$ is 140 mEq/L, $[Cl^-]$ is 105 mEq/L, and $[HCO_3^-]$ is 24 mEq/L, the anion gap is 11 mEq/L. If an acid such as lactic acid is added to plasma, the reaction lactic acid + HCO_3^- ⇌ lactate$^-$ + H_2O + CO_2 will be pushed to the right. Consequently, the plasma $[HCO_3^-]$ will be decreased and because the $[Cl^-]$ is not changed, the anion gap will be increased. The unmeasured anion in this case is lactate. In several types of metabolic acidosis, the low blood pH is accompanied by a high anion gap (Table 25.5). (These can be remembered from the mnemonic MULEPAKS formed from the first letters of this list.) In other types of metabolic acidosis, the low blood pH is accompanied by a normal anion gap (see Table 25.5). For example, with diarrhea and a loss of alkaline intestinal fluid, plasma $[HCO_3^-]$ falls but plasma $[Cl^-]$ rises, and the two changes counterbalance each other so the anion gap is unchanged. Again, the chief value of the anion gap concept is that it allows a clinician to narrow down possible explanations for metabolic acidosis in a patient.

Metabolic Alkalosis Results From a Gain of Strong Base or Bicarbonate or a Loss of Noncarbonic Acid

Metabolic alkalosis is an abnormal process characterized by a gain of a strong base or HCO_3^- or a loss of an acid (other than carbonic acid). Plasma $[HCO_3^-]$ and pH rise; P_{CO_2} rises because of respiratory compensation. These changes are opposite to those seen in metabolic acidosis (see Table 25.3). A variety of situations can produce metabolic alkalosis, including the ingestion of antacids, vomiting of gastric acid juice, and enhanced renal H^+ loss (e.g., as a result of hyperaldosteronism or hypokalemia). Clinical Focus Box 25.3 discusses the metabolic alkalosis produced by vomiting of gastric juice.

Chemical Buffering. Chemical buffers in the body limit the alkaline shift in blood pH by releasing H^+ as they are titrated in the alkaline direction. About one third of the buffering occurs in cells.

Respiratory Compensation. The respiratory compensation for metabolic alkalosis is hypoventilation. An alkaline blood pH inhibits ventilation. Hypoventilation raises the blood P_{CO_2} and $[H_2CO_3]$, reducing the alkaline shift in pH. A 1 mEq/L rise in plasma $[HCO_3^-]$ caused by metabolic alkalosis is accompanied by a 0.7 mm Hg rise in P_{CO_2} (see Table 25.4). If, for example, the plasma $[HCO_3^-]$ rose to 40 mEq/L, what would the plasma pH be with and without respiratory compensation? With respiratory compensation, the P_{CO_2} should rise by 11.2 mm Hg (0.7 × 16) to 51.2 mm Hg ($[CO_{2(d)}]$ = 1.54 mmol/L). The pH is 7.51:

$$pH = 6.10 + \log \frac{[40]}{[1.54]} = 7.51 \qquad (41)$$

Without respiratory compensation, the pH would be 7.62:

$$pH = 6.10 + \log \frac{[40]}{[1.2]} = 7.62 \qquad (42)$$

Respiratory compensation for metabolic alkalosis is limited because hypoventilation leads to hypoxia and CO_2 retention, and both increase breathing.

Renal Compensation. The kidneys respond to metabolic alkalosis by lowering the plasma $[HCO_3^-]$. The plasma $[HCO_3^-]$ is primarily raised and more HCO_3^- is filtered than can be reabsorbed (see Fig. 25.7); in addition, HCO_3^- is secreted in the collecting ducts. Both of these changes lead to increased urinary $[HCO_3^-]$ excretion. If the cause of the metabolic alkalosis is corrected, the kidneys can often restore the plasma $[HCO_3^-]$ and pH to normal in a day or two.

TABLE 25.5 High and Normal Anion Gap Metabolic Acidosis

Condition	Explanation
High anion gap metabolicacidosis	
Methanol intoxication	Methanol metabolized to formic acid
Uremia	Sulfuric, phosphoric, uric, and hippuric acids retained due to renal failure
Lactic acid	Lactic acid buffered by HCO_3^- and accumulates as lactate
Ethylene glycol intoxication	Ethylene glycol metabolized to glyoxylic, glycolic, and oxalic acids
p-Aldehyde intoxication	*p*-Aldehyde metabolized to acetic and chloroacetic acids
Ketoacidosis	Production of β-hydroxybutyric and acetoacetic acids
Salicylate intoxication	Impaired metabolism leads to production of lactic acid and ketone body acids; accumulation of salicylate
Normal anion gap metabolic acidosis	
Diarrhea	Loss of HCO_3^- in stool; kidneys conserve Cl^-
Renal tubular acidosis	Loss of HCO_3^- in urine or inadequate excretion of H^+; kidneys conserve Cl^-
Ammonium chloride ingestion	NH_4^+ is converted to urea in liver, a process that consumes HCO_3^-; excess Cl^- is ingested

CLINICAL FOCUS BOX 25.3

Vomiting and Metabolic Alkalosis

Vomiting of gastric acid juice results in **metabolic alkalosis** and fluid and electrolyte disturbances. Gastric acid juice contains about 0.1 M HCl. The acid is secreted by stomach parietal cells; these cells have an H^+/K^+-ATPase in their luminal plasma membrane and a Cl^-/HCO_3^- exchanger in their basolateral plasma membrane. When HCl is secreted into the stomach lumen and lost to the outside, there is a net gain of HCO_3^- in the blood plasma and no change in the anion gap. The HCO_3^-, in effect, replaces lost plasma Cl^-.

Ventilation is inhibited by the alkaline blood pH, resulting in a rise in P_{CO_2}. This respiratory compensation for the metabolic alkalosis, however, is limited because hypoventilation leads to a rise in P_{CO_2} and a fall in P_{O_2}, both of which stimulate breathing.

The logical renal compensation for metabolic alkalosis is enhanced excretion of HCO_3^-. In people with persistent vomiting, however, the urine is sometimes acidic and renal HCO_3^-reabsorption is enhanced, maintaining an elevated plasma [HCO_3^-]. This situation occurs because vomiting is accompanied by losses of ECF and K^+. Fluid loss leads to a decrease in effective arterial blood volume and engagement of mechanisms that reduce Na^+ excretion, such as decreased GFR and increased plasma renin, angiotensin, and aldosterone levels (see Chapter 24). Aldosterone stimulates H^+ secretion by collecting duct α-intercalated cells. Renal tubular Na^+/H^+ exchange is stimulated by volume depletion because the tubules reabsorb Na^+ more avidly than usual. With more H^+ secretion, more new HCO_3^- is added to the blood. The kidneys reabsorb filtered HCO_3^- completely, even though plasma HCO_3^- level is elevated, and maintain the metabolic alkalosis.

Vomiting results in K^+ depletion because of a loss of K^+ in the vomitus, decreased food intake and, most important quantitatively, enhanced renal K^+ excretion. Extracellular alkalosis results in a shift of K^+ into cells (including renal cells) and, thereby, promotes K^+ secretion and excretion. Elevated plasma aldosterone levels also favor K^+ loss in the urine.

Treatment of metabolic alkalosis primarily depends on eliminating the cause of vomiting. Correction of the alkalosis by administering an organic acid, such as lactic acid, does not make sense because this acid would simply be converted to CO_2 and H_2O; this approach also does not address the Cl^- deficit. The ECF volume depletion and the Cl^- and K^+ deficits can be corrected by administering isotonic saline and appropriate amounts of KCl. Because replacement of Cl^- is a key component of therapy, this type of metabolic alkalosis is said to be "chloride-responsive." After Na^+, Cl^-, water, and K^+ deficits have been replaced, excess HCO_3^- (accompanied by surplus Na^+) will be excreted in the urine, and the kidneys will return blood pH to normal.

Clinical Evaluation of Acid-Base Disturbances Requires a Comprehensive Study

Acid-base data should always be interpreted in the context of other information about a patient. A complete history and physical examination provide important clues to possible reasons for an acid-base disorder.

To identify an acid-base disturbance from laboratory values, it is best to look first at the pH. A low blood pH indicates acidosis; a high blood pH indicates alkalosis. If acidosis is present, for example, it could be either respiratory or metabolic. A low blood pH and elevated P_{CO_2} point to respiratory acidosis; a low pH and low plasma [HCO_3^-] indicate metabolic acidosis. If alkalosis is present, it could be either respiratory or metabolic. A high blood pH and low plasma P_{CO_2} indicate respiratory alkalosis; a high blood pH and high plasma [HCO_3^-] indicate metabolic alkalosis.

Whether the body is making an appropriate response for a simple acid-base disorder can be judged from the values in Table 25.4. Inappropriate values suggest that more than one acid-base disturbance may be present. Patients may have two or more of the four simple acid-base disturbances at the same time; in which case, they have a **mixed acid-base disturbance**.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. If the pK_a of NH_4^+ is 9.0, the ratio of NH_3 to NH_4^+ in a urine sample with a pH of 6.0 is
   (A) 1:3
   (B) 3:1
   (C) 3:2
   (D) 1:1,000
   (E) 1,000:1
2. An arterial blood sample taken from a patient has a pH of 7.32 ($[H^+]$ = 48 nmol/L) and P_{CO_2} of 24 mm Hg. What is the plasma [HCO_3^-]?
   (A) 6 mEq/L
   (B) 12 mEq/L
   (C) 20 mEq/L
   (D) 24 mEq/L
   (E) 48 mEq/L
3. Which segment can establish the steepest pH gradient (tubular fluid-to-blood)?
   (A) Proximal convoluted tubule
   (B) Thin ascending limb
   (C) Thick ascending limb
   (D) Distal convoluted tubule
   (E) Collecting duct
4. Most of the hydrogen ions secreted by the kidney tubules are
   (A) Consumed in the reabsorption of filtered bicarbonate
   (B) Excreted in the urine as ammonium ions
   (C) Excreted in the urine as free hydrogen ions
   (D) Excreted in the urine as titratable acid

(continued)

5. The following measurements were made in a healthy adult:

Filtered bicarbonate	4,320 mEq/day
Excreted bicarbonate	2 mEq/day
Urinary titratable acid	30 mEq/day
Urinary ammonia (NH_4^+)	60 mEq/day
Urine pH	5

Net acid excretion by the kidneys is
(A) 28 mEq/day
(B) 30 mEq/day
(C) 88 mEq/day
(D) 90 mEq/day
(E) 92 mEq/day

6. If a patient with uncontrolled diabetes mellitus has a daily excretion rate of 200 mEq of titratable acid and 500 mEq of NH_4^+, how many mEq of new HCO_3^- have the kidney tubules added to the blood?
(A) 0 mEq
(B) 200 mEq
(C) 300 mEq
(D) 500 mEq
(E) 700 mEq

7. Which of the following causes increased tubular secretion of hydrogen ions?
(A) A decrease in arterial P_{CO_2}
(B) Adrenal cortical insufficiency
(C) Administration of a carbonic anhydrase inhibitor
(D) An increase in intracellular pH
(E) An increase in tubular sodium reabsorption

8. A homeless woman was found on a hot summer night lying on a park bench in a comatose condition. An arterial blood sample revealed a pH of 7.10, P_{CO_2} of 20 mm Hg, and plasma [HCO_3^-] of 6 mEq/L. Plasma glucose and blood urea nitrogen (BUN) values were normal. Plasma [Na^+] was 140 mEq/L and [Cl^-] was 105 mEq/L. Which of the following might explain her condition?
(A) Acute renal failure
(B) Diarrhea as a result of food poisoning
(C) Methanol intoxication
(D) Overdose with a drug that produces respiratory depression
(E) Uncontrolled diabetes mellitus

9. Which of the following arterial blood values might be expected in a mountain climber who has been residing at a high-altitude base camp below the summit of Mt. Everest for one week?

	pH	Po2 (mm Hg)	Pco2 (mm Hg)	Plasma [HCO32] (mEq/L)
(A)	7.18	95	25	9
(B)	7.35	50	60	32
(C)	7.53	40	20	16
(D)	7.53	95	50	40
(E)	7.62	40	20	20

10. A 25-year-old nurse is brought to the emergency department shortly before midnight. Although somewhat drowsy, she was able to relate that she had attempted to kill herself by swallowing the contents of a bottle of aspirin tablets a few hours before. Which of the following set of arterial blood values is expected?

	pH	Po2 (mm Hg)	Pco2 (mm Hg)	Plasma [HCO32] (mEq/L)
(A)	7.25	95	19	8
(B)	7.29	55	60	28
(C)	7.40	95	40	24
(D)	7.59	95	16	15
(E)	7.70	95	16	19

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CASE STUDIES FOR PART IV • • •

CASE STUDY FOR CHAPTER 23

Nephrotic Syndrome

A 6-year-old boy is brought to the pediatrician by his mother because of a puffy face and lethargy. A few weeks before, he had an upper respiratory tract infection, probably caused by a virus. Body temperature is 36.8°C; blood pressure, 95/65; and heart rate, 90 beats/min. Puffiness around the eyes, abdominal swelling, and pitting edema in the legs are observed. A urine sample (dipstick) is negative for glucose but reveals 3+ protein. Microscopic examination of the urine reveals no cellular elements or casts. Plasma [Na^+] is 140 mEq/L; BUN, 10 mg/dL; [glucose], 100 mg/dL; creatinine, 0.8 mg/dL; serum albumin, 2.3 g/dL (normal, 3.0 to 4.5 g/dL); and cholesterol, 330 mg/dL. A 24-hour urine sample has a volume of 1.10 L and contains 10 mEq/L Na^+, 60 mg/dL creatinine, and 0.8 g/dL protein.

The child is treated with the corticosteroid prednisone, and the edema and proteinuria disappear in 2 weeks. Puffiness and proteinuria recur 4 months later, and a renal biopsy is performed. Glomeruli are normal by light microscopy, but effacement of podocyte foot processes and loss of filtration slits is seen with the electron microscope. No immune deposits or complement are seen after immunostaining. The biopsy indicates minimal change glomerulopathy. The podocyte cell surface and glomerular basement membrane show reduced staining with a cationic dye.

Questions

1. What features in this case would cause suspicion of nephrotic syndrome?
2. What is the explanation for the proteinuria?
3. Why does the abnormally high rate of urinary protein excretion underestimate the rate of renal protein loss?
4. What is the endogenous creatinine clearance, and is it normal? (The boy's body surface area is 0.86 m^2.)
5. What is the explanation for the edema?

Answers to Case Study Questions for Chapter 23

1. The child has the classical feature of nephrotic syndrome: heavy proteinuria (8.8 g/day), hypoalbuminemia (<3 g/dL), generalized edema, and hyperlipidemia (plasma cholesterol 330 mg/dL).

2. Proteinuria is a consequence of an abnormally high permeability of the glomerular filtration barrier to the normal plasma proteins. This condition might be a result of an increased size of "holes" or pores in the basement membrane and filtration slit diaphragms. The decreased staining with a cationic dye, however, suggests that there was a loss of fixed negative charges from the filtration barrier. Recall that serum albumin bears a net negative charge at physiological pH values, and that negative charges associated with the glomerular filtration barrier impede filtration of this plasma protein.
3. Proteins that have leaked across the glomerular filtration barrier are not only excreted in the urine but are reabsorbed by proximal tubules. The endocytosed proteins are digested in lysosomes to amino acids, which are returned to the circulation. Both increased renal catabolism by tubule cells and increased excretion of serum albumin in the urine contribute to the hypoalbuminemia. The liver, which synthesizes serum albumin, cannot keep up with the renal losses.
4. The endogenous creatinine (CR) clearance (an estimate of GFR) equals $(U_{CR} \times V)/P_{CR} = (60 \times 1.10)/0.8 = 82$ L/day. Normalized to a standard body surface area of 1.73 m^2, C_{CR} is 166 L/day $-1.73\ m^2$, which falls within the normal range (150 to 210 L/day $-1.73\ m^2$). Note that the permeability of the glomerular filtration barrier to macromolecules (plasma proteins) was abnormally high, but permeability to fluid was not increased. In some patients, a loss of filtration slits may be significant and may lead to a reduced fluid permeability and GFR.
5. The edema is a result of altered capillary Starling forces and renal retention of salt and water. The decline in plasma [protein] lowers the plasma colloid osmotic pressure, favoring fluid movement out of the capillaries into the interstitial compartment. The edema is particularly noticeable in the soft skin around the eyes (periorbital edema). The abdominal distension (in the absence of organ enlargement) suggests ascites (an abnormal accumulation of fluid in the abdominal cavity). The kidneys avidly conserve Na^+ (note the low urine [Na^+]) despite an expanded ECF volume. Although the exact reasons for renal Na^+ retention are controversial, a decrease in the effective arterial blood volume may be an important stimulus (see Chapter 24). This leads to activation of the renin-angiotensin-aldosterone system and stimulation of the sympathetic nervous system, both of which favor renal Na^+ conservation. In addition, distal segments of the nephron reabsorb more Na^+ than usual because of an intrinsic change in the kidneys.

Reference

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Case Study for Chapter 24

Water Intoxication

A 60-year-old woman with a long history of mental illness was institutionalized after a violent argument with her son. She experiences visual and auditory hallucinations and, on one occasion, ran naked through the ward screaming. She refuses to eat anything since admission, but maintains a good fluid intake. On the fifth hospital day, she complains of a slight headache and nausea and has three episodes of vomiting. Later in the day, she is found on the floor in a semiconscious state, confused and disoriented. She is pale and had cool extremities. Her pulse rate is 70/min and blood pressure is 150/100 mm Hg. She is transferred to a general hospital and, during transfer, has three grand mal seizures and arrives in a semiconscious, uncooperative state. A blood sample reveals a plasma [Na^+] of 103 mEq/L. Urine osmolality is 362 mOsm/kg H_2O and urine [Na^+] is 57 mEq/L. She is given an intravenous infusion of hypertonic saline (1.8% NaCl) and placed on water restriction. Several days after she had improved, bronchoscopy is performed.

Questions

1. What is the likely cause of the severe hyponatremia?
2. How much of an increase in plasma [Na^+] would an infusion of 1 L of 1.8% NaCl (308 mEq Na^+/L) produce? Assume that her total body water is 25 L (50% of her body weight). Why is the total body water used as the volume of distribution of Na^+, even though the administered Na^+ is limited to the ECF compartment?
3. Why is the brain so profoundly affected by hypoosmolality? Why should the hypertonic saline be administered slowly?
4. Why was the bronchoscopy performed?

Answers to Case Study Questions for Chapter 24

1. The problem started with ingestion of excessive amounts of water. Compulsive water drinking is a common problem in psychotic patients. The increased water intake, combined with an impaired ability to dilute the urine (note the inappropriately high urine osmolality), led to severe hyponatremia and water intoxication.
2. Addition of 1 L of 308 mEq Na^+/L to 25 L produces an increase in plasma [Na^+] of 12 mEq/L. The total body water is used in this calculation because when hypertonic NaCl is added to the ECF, it causes the movement of water out of the cell compartment, diluting the extracellular Na^+.
3. Because the brain is enclosed in a nondistensible cranium, when water moves into brain cells and causes them to swell, intracranial pressure can rise to very high values. This can damage nervous tissue directly or indirectly by impairing cerebral blood flow. The neurological symptoms seen in this patient (headache, semiconsciousness, grand mal seizures) are consequences of brain swelling. The increased blood pressure and cool and pale skin may be a consequence of sympathetic nervous system discharge resulting from increased intracranial pressure. Too rapid restoration of a normal plasma [Na^+] can produce serious damage to the brain (central pontine myelinolysis).
4. The physicians wanted to exclude the presence of a bronchogenic tumor, which is the most common cause of SIADH. No abnormality was detected. Today, a computed tomography (CT) scan would be performed first.

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Case Study for Chapter 25

Lactic Acidosis and Hemorrhagic Shock

During a violent argument over money, a 30-year-old man was stabbed in the stomach. The assailant escaped, but friends were able to rush the victim by car to the county hospital. The patient is unconscious, with a blood pressure (mm Hg) of 55/35 and heart rate of 165 beats/minute. Breathing is rapid and shallow. The subject is pale, with cool, clammy skin. On admission, about

an hour after the stabbing, an arterial blood sample is taken, and the following data were reported:

	Patient	*Normal Range*
Glucose	125 mg/dL	70–110 mg/dL (3.9–6.1 mmol/L) (fasting values)
Na^+	140 mEq/L	136–145 mEq/L
K^+	4.8 mEq/L	3.5–5.0 mEq/L
Cl^-	103 mEq/L	95–105 mEq/L
HCO_3^-	4 mEq/L	22–26 mEq/L
BUN	23 mg/dL	7–18 mg/dL (1.2–3.0 mmol/L urea nitrogen)
Creatinine	1.1 mg/dL	0.6–1.2 mg/dL (53–106 μmol/L)
pH	7.08	7.35–7.45
P_{aCO_2}	14	35–45 mm Hg
P_{aO_2}	97 mm Hg	75–105 mm Hg
Hematocrit	35%	41–53%

Questions

1. What type of acid-base disturbance is present?
2. What is the reason for the low P_{aCO_2}?
3. Calculate the plasma anion gap and explain why it is high.
4. Why is the hematocrit low?
5. Discuss the status of kidney function.
6. What is the most appropriate treatment for the acid-base disturbance?

Answers to Case Study Questions for Chapter 25

1. The subject has a metabolic acidosis, with an abnormally low arterial blood pH and plasma [HCO_3^-].
2. The low P_{aCO_2} is a result of respiratory compensation. Ventilation is stimulated by the low blood pH, sensed by the peripheral chemoreceptors.
3. The anion gap is = [Na^+] − [Cl^-] − [HCO_3^-] = 140 − 103 − 4 = 33 mEq/L, which is abnormally high. Considering the history and physical findings, the high anion gap is most likely caused by inadequate tissue perfusion, with resultant anaerobic metabolism and production of lactic acid. The lactic acid is buffered by HCO_3^- and lactate accumulates as the unmeasured anion. Note that tissue hypoxia can occur if blood flow is diminished, even when arterial P_{O_2} is normal.
4. The low hematocrit is a result of absorption of interstitial fluid by capillaries, consequent to the hemorrhage, low arterial blood pressure, and low capillary hydrostatic pressure.
5. In response to the blood loss and low blood pressure, kidney blood flow and GFR would be drastically reduced. The sympathetic nervous system, combined with increased plasma levels of AVP and angiotensin II, would produce intense renal vasoconstriction. The hydrostatic pressure in the glomeruli would be so low that practically no plasma would be filtered and little urine (oliguria) or no urine (anuria) would be excreted. Because of the short duration of renal shutdown, plasma [creatinine] is still in the normal range; the elevated BUN is probably mainly a result of bleeding into the gastrointestinal tract, digestion of blood proteins, and increased urea production.
6. Control of bleeding and administration of whole blood (or isotonic saline solutions and packed red blood cells) would help restore the circulation. With improved tissue perfusion, the lactate will be oxidized to HCO_3^-.