

CHAPTER 31

UNIT V

Acid–Base Regulation

The regulation of hydrogen ion (H^+) balance is similar in some ways to the regulation of other ions in the body. For example, there must be a balance between the intake or production of H^+ and the net removal of H^+ from the body to achieve homeostasis. And, as is true for other ions, the kidneys play a key role in regulating H^+ removal from the body. However, precise control of extracellular fluid H^+ concentration involves much more than the simple elimination of H^+ by the kidneys. Multiple acid–base buffering mechanisms involving the blood, cells, and lungs also are essential in maintaining normal H^+ concentrations in extracellular and intracellular fluids.

In this chapter, we consider the mechanisms that regulate H^+ concentration, with special emphasis on renal H^+ secretion and renal reabsorption, production, and excretion of bicarbonate ions (HCO_3^-), one of the key components of acid–base control systems in the body fluids.

HYDROGEN ION CONCENTRATION IS PRECISELY REGULATED

Precise H^+ regulation is essential because the activities of almost all enzyme systems in the body are influenced by H^+ concentration. Therefore, changes in H^+ concentration alter virtually all cell and body functions.

Compared with other ions, the H^+ concentration of the body fluids normally is kept at a low level. For example, the concentration of sodium in extracellular fluid (142 mEq/L) is about 3.5 million times as great as the normal concentration of H^+, which averages only 0.00004 mEq/L. Equally important, the normal variation in H^+ concentration in extracellular fluid is only about one millionth as great as the normal variation in sodium ion (Na^+) concentration. Thus, the precision with which H^+ is regulated emphasizes its importance to the various cell functions.

ACIDS AND BASES—DEFINITIONS AND MEANINGS

A hydrogen ion is a single free proton released from a hydrogen atom. Molecules containing hydrogen atoms that can release hydrogen ions in a solution are referred to as *acids*. An example is hydrochloric acid (HCl), which ionizes in water to form hydrogen ions (H^+) and chloride ions (Cl^-). Likewise, carbonic acid (H_2CO_3) ionizes in water to form H^+ and bicarbonate ions (HCO_3^-).

A *base* is an ion or a molecule that can accept an H^+. For example, HCO_3^- is a base because it can combine with H^+ to form H_2CO_3. Likewise, $HPO_4^=$ is a base because it can accept an H^+ to form $H_2PO_4^-$. The proteins in the body also function as bases because some of the amino acids that make up proteins have net negative charges that readily accept H^+. The protein *hemoglobin* in the red blood cells and proteins in the other cells of the body are among the most important of the body's bases.

The terms *base* and *alkali* are often used synonymously. An *alkali* is a molecule formed by the combination of one or more of the alkaline metals—such as sodium, potassium, and lithium—with a highly basic ion such as a hydroxyl ion (OH^-). The base portion of these molecules reacts quickly with H^+ to remove it from solution and are, therefore, typical bases. For similar reasons, the term *alkalosis* refers to the excess removal of H^+ from the body fluids, in contrast to the excess addition of H^+, which is referred to as *acidosis.*

Strong and Weak Acids and Bases. A strong acid, such as HCl, rapidly dissociates and releases especially large amounts of H^+ in solution. Weak acids such as H_2CO_3 are less likely to dissociate their ions and, therefore, release H^+ with less vigor. A strong base is one that reacts rapidly and strongly with H^+ and, therefore, quickly removes H^+ from a solution. A typical example is OH^-, which reacts with H^+ to form water (H_2O). A typical weak base is HCO_3^- because it binds with H^+ much more weakly than OH^-. Most acids and bases in the extracellular fluid that are involved in normal acid–base regulation are weak acids and bases. The most important ones that we discuss are carbonic acid (H_2CO_3) and HCO_3^- base.

Normal H^+ Concentration and pH of Body Fluids and Changes That Occur in Acidosis and Alkalosis. The blood H^+ concentration is normally maintained within tight limits around a normal value of about 0.00004

mEq/L (40 nEq/L). Normal variations are only about 3 to 5 nEq/L but, under extreme conditions, the H^+ concentration can vary from as low as 10 nEq/L to as high as 160 nEq/L without resulting in death.

Because H^+ concentration normally is low, and because these small numbers are cumbersome, it is customary to express H^+ concentration on a logarithm scale using pH units. pH is related to the actual H^+ concentration by the following formula (H^+ concentration $[H^+]$ is expressed in *equivalents* per liter):

$$pH = \log \frac{1}{[H^+]} = -\log [H^+]$$

For example, normal $[H^+]$ is 40 nEq/L (0.00000004 Eq/L). Therefore, the normal pH is as follows:

$$pH = -\log [0.00000004]$$
$$pH = 7.4$$

From this formula, one can see that pH is inversely related to the H^+ concentration; therefore, a low pH corresponds to a high H^+ concentration, and a high pH corresponds to a low H^+ concentration.

The normal pH of arterial blood is 7.4, whereas the pH of venous blood and interstitial fluids is about 7.35 because of the extra amounts of carbon dioxide (CO_2) released from the tissues to form H_2CO_3 in these fluids (**Table 31-1**). Because the normal pH of arterial blood is 7.4, a person is considered to have *acidemia* when the pH falls significantly below this value and *alkalemia* when the pH rises above 7.4. The lower limit of pH at which a person can live more than a few hours is about 6.8, and the upper limit is about 8.0.

Intracellular pH usually is slightly lower than plasma pH because cell metabolism produces acid, especially H_2CO_3. Depending on the type of cells, the pH of intracellular fluid has been estimated to range between 6.0 and 7.4. Hypoxia of the tissues and poor blood flow to the tissues can cause acid accumulation and decreased intracellular pH. The terms *acidosis* and *alkalosis* describe the processes that lead to acidemia and alkalemia, respectively.

The pH of urine can range from 4.5 to 8.0, depending on the acid–base status of the extracellular fluid. As discussed later, the kidneys play a major role in correcting abnormalities of extracellular fluid H^+ concentration by excreting acids or bases at variable rates.

Table 31-1 pH and H^+ Concentration of Body Fluids

	H^+ Concentration (mEq/L)	pH
Extracellular Fluid		
• Arterial blood	• 4.0×10^{-5}	• 7.40
• Venous blood	• 4.5×10^{-5}	• 7.35
• Interstitial fluid	• 4.5×10^{-5}	• 7.35
Intracellular fluid	1×10^{-3} to 4×10^{-5}	6.0–7.4
Urine	3×10^{-2} to 1×10^{-5}	4.5–8.0
Gastric HCl	160	0.8

An extreme example of an acidic body fluid is the HCl secreted into the stomach by the *oxyntic (parietal)* cells of the stomach mucosa, as discussed in Chapter 65. The H^+ concentration in these cells is about 4 million times greater than the hydrogen concentration in blood, with a pH of 0.8. In the remainder of this chapter, we discuss the regulation of extracellular fluid H^+ concentration.

DEFENDING AGAINST CHANGES IN H^+ CONCENTRATION: BUFFERS, LUNGS, AND KIDNEYS

Three primary systems regulate the H^+ concentration in the body fluids: (1) the *chemical acid–base buffer systems of the body fluids*, which immediately combine with an acid or a base to prevent excessive changes in H^+ concentration; (2) the *respiratory center*, which regulates the removal of CO_2 (and, therefore, H_2CO_3) from the extracellular fluid; and (3) the *kidneys*, which can excrete acidic or alkaline urine, thereby readjusting the extracellular fluid H^+ concentration toward normal during acidosis or alkalosis.

When there is a change in H^+ concentration, the *buffer systems* of the body fluids react within seconds to minimize these changes. Buffer systems do not eliminate H^+ from or add H^+ to the body but only keep them tied up until balance can be re-established.

The second line of defense, the *respiratory system*, acts within a few minutes to eliminate CO_2 and, therefore, H_2CO_3 from the body.

These first two lines of defense keep the H^+ concentration from changing too much until the more slowly responding third line of defense, the *kidneys*, can eliminate the excess acid or base from the body. Although the kidneys are relatively slow to respond compared with the other defenses, over a period of hours to several days, they are by far the most powerful of the acid–base regulatory systems.

BUFFERING OF H^+ IN THE BODY FLUIDS

A buffer is any substance that can reversibly bind H^+. The general form of the buffering reaction is as follows:

$$\text{Buffer} + H^+ \rightleftharpoons H\,\text{Buffer}$$

In this example, a free H^+ combines with the buffer to form a weak acid (H buffer) that can either remain as an unassociated molecule or dissociate back to the buffer and H^+. When the H^+ concentration increases, the reaction is forced to the right, and more H^+ binds to the buffer, as long as buffer is available. Conversely, when the H^+ concentration decreases, the reaction shifts toward the left, and H^+ is released from the buffer. In this way, changes in H^+ concentration are minimized.

The importance of the body fluid buffers can be quickly realized if one considers the low concentration of H^+ in the body fluids and the relatively large amounts

of acids produced by the body each day. About 80 milliequivalents of H^+ is ingested or produced each day by metabolism, whereas the H^+ concentration of the body fluids normally is only about 0.00004 mEq/L. Without buffering, the daily production and ingestion of acids would cause lethal changes in the body fluid H^+ concentration.

The action of acid–base buffers can perhaps best be explained by considering the buffer system that is quantitatively the most important in the extracellular fluid—the bicarbonate buffer system.

BICARBONATE BUFFER SYSTEM

The bicarbonate buffer system consists of a water solution that contains two ingredients: (1) a weak acid, H_2CO_3; and (2) a bicarbonate salt, such as sodium bicarbonate ($NaHCO_3$).

H_2CO_3 is formed in the body by the reaction of CO_2 with H_2O:

$$CO_2 + H_2O \xleftrightarrow[\text{anhydrase}]{\text{Carbonic}} H_2CO_3$$

This reaction is slow, and exceedingly small amounts of H_2CO_3 are formed unless the enzyme *carbonic anhydrase* is present. This enzyme is especially abundant in the walls of the lung alveoli, where CO_2 is released; carbonic anhydrase is also present in the epithelial cells of the renal tubules, where CO_2 reacts with H_2O to form H_2CO_3.

H_2CO_3 ionizes weakly to form small amounts of H^+ and HCO_3^-:

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

The second component of the system, bicarbonate salt, occurs predominantly as $NaHCO_3$ in the extracellular fluid. $NaHCO_3$ ionizes almost completely to form HCO_3^- and Na^+, as follows:

$$NaHCO_3 \rightleftharpoons Na^+ + HCO_3^-$$

Now, putting the entire system together, we have the following:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + \underbrace{HCO_3^-}_{+\ Na^+}$$

Because of the weak dissociation of H_2CO_3, the H^+ concentration is extremely low.

When a strong acid such as HCl is added to the bicarbonate buffer solution, the increased H^+ released from the acid ($HCl \rightarrow H^+ + Cl^-$) is buffered by HCO_3^-:

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

As a result, more H_2CO_3 is formed, causing increased CO_2 and H_2O production. From these reactions, one can see that H^+ from the strong acid HCl reacts with HCO_3^- to form the very weak acid H_2CO_3, which in turn forms CO_2 and H_2O. The excess CO_2 greatly stimulates respiration, which eliminates the CO_2 from the extracellular fluid.

The opposite reactions take place when a strong base, such as sodium hydroxide (NaOH), is added to the bicarbonate buffer solution.

$$NaOH + H_2CO_3 \rightarrow NaHCO_3 + H_2O$$

In this case, the OH^- from the NaOH combines with H_2CO_3 to form additional HCO_3^-. Thus, the weak base $NaHCO_3$ replaces the strong base NaOH. At the same time, the concentration of H_2CO_3 decreases (because it reacts with NaOH), causing more CO_2 to combine with H_2O to replace the H_2CO_3:

$$\begin{array}{ccccc} CO_2 + H_2O & \longrightarrow & H_2CO_3 & \longrightarrow & \uparrow HCO_3^- + H^+ \\ & & + & & + \\ & & NaOH & & Na \end{array}$$

The net result, therefore, is a tendency for the CO_2 levels in the blood to decrease, but the decreased CO_2 in the blood inhibits respiration and decreases the rate of CO_2 expiration. The rise in blood HCO_3^- concentration that occurs is compensated for by increased renal excretion of HCO_3^-.

Quantitative Dynamics of the Bicarbonate Buffer System

All acids, including H_2CO_3, are ionized to some extent. From mass balance considerations, the concentrations of H^+ and HCO_3^- are proportional to the concentration of H_2CO_3:

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

For any acid, the concentration of the acid relative to its dissociated ions is defined by the *dissociation constant, K′*.

$$K' = \frac{H^+ \times HCO_3^-}{H_2CO_3} \quad (1)$$

This equation indicates that in an H_2CO_3 solution, the amount of free H^+ is equal to

$$H^+ = K' \times \frac{H_2CO_3}{HCO_3^-} \quad (2)$$

The concentration of undissociated H_2CO_3 cannot be measured in solution because it rapidly dissociates into CO_2 and H_2O or into H^+ and HCO_3^-. However, the CO_2 dissolved in the blood is directly proportional to the amount of undissociated H_2CO_3. Therefore, Equation 2 can be rewritten as follows:

$$H^+ = K \times \frac{CO_2}{HCO_3^-} \quad (3)$$

The dissociation constant (K) for Equation 3 is only about 1/400 of the dissociation constant (K′) of Equation 2 because the proportionality ratio between H_2CO_3 and CO_2 is 1:400.

Equation 3 is written in terms of the total amount of CO_2 dissolved in solution. However, most clinical laboratories measure the blood CO_2 tension (P_{CO_2}) rather than the actual amount of CO_2. Fortunately, the amount of CO_2 in the blood is a linear function of P_{CO_2} multiplied by the solubility coefficient for CO_2; under physiological conditions, the solubility coefficient for CO_2 is 0.03 mmol/mm Hg at body temperature. This means that 0.03 millimole of H_2CO_3 is present in the blood for each mm Hg P_{CO_2} measured. Therefore, Equation 3 can be rewritten as

$$H^+ = K \times \frac{(0.03 \times P_{CO_2})}{HCO_3^-} \quad (4)$$

Henderson-Hasselbalch Equation. As discussed earlier, it is customary to express the H^+ concentration in pH units rather than in actual concentrations. Recall that pH = $-\log H^+$.

The dissociation constant (pK) can be expressed in a similar manner.

$$pK = -\log K$$

Therefore, we can express the H^+ concentration in Equation 4 in pH units by taking the negative logarithm of that equation, which yields the following:

$$-\log H^+ = -\log pK - \log \frac{(0.03 \times P_{CO_2})}{HCO_3^-} \quad (5)$$

Therefore,

$$pH = pK - \log \frac{(0.03 \times P_{CO_2})}{HCO_3^-} \quad (6)$$

Rather than work with a negative logarithm, we can change the sign of the logarithm and invert the numerator and denominator in the last term, using the law of logarithms, to yield the following:

$$pH = pK + \log \frac{HCO_3^-}{(0.03 \times P_{CO_2})} \quad (7)$$

For the bicarbonate buffer system, the pK is 6.1, and Equation 7 can be written as follows:

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times P_{CO_2}} \quad (8)$$

Equation 8 is the Henderson-Hasselbalch equation and, with it, one can calculate the pH of a solution if the molar concentration of HCO_3^- and the P_{CO_2} are known.

From the Henderson-Hasselbalch equation, it is apparent that an increase in HCO_3^- concentration causes the pH to rise, shifting the acid–base balance toward alkalosis. An increase in P_{CO_2} causes the pH to decrease, shifting the acid–base balance toward acidosis.

The Henderson-Hasselbalch equation, in addition to defining the determinants of normal pH regulation and acid–base balance in the extracellular fluid, provides insight into the physiological control of the acid and base composition of the extracellular fluid. As discussed later, *the HCO_3^- concentration is regulated mainly by the kidneys, whereas the P_{CO_2} in extracellular fluid is controlled by the rate of respiration.* By increasing the rate of respiration, the lungs remove CO_2 from the plasma and, by decreasing respiration, the lungs elevate P_{CO_2}. Normal physiological acid–base homeostasis results from the coordinated efforts of both the lungs and kidneys, and acid–base disorders occur when one or both of these control mechanisms are impaired, thus altering either the HCO_3^- concentration or P_{CO_2} of extracellular fluid.

When disturbances of acid–base balance result from a primary change in extracellular fluid HCO_3^- concentration, they are referred to as *metabolic* acid–base disorders. Therefore, acidosis caused by a primary decrease in HCO_3^- concentration is termed *metabolic acidosis*, whereas alkalosis caused by a primary increase in HCO_3^- concentration is called *metabolic alkalosis*. Acidosis caused by an increase in P_{CO_2} is called *respiratory acidosis*, whereas alkalosis caused by a decrease in P_{CO_2} is termed *respiratory alkalosis*.

Bicarbonate Buffer System Titration Curve. Figure 31-1 shows the changes in pH of the extracellular fluid when the ratio of HCO_3^- to CO_2 in extracellular fluid is altered. When the concentrations of these two components are equal, the right-hand portion of Equation 8 becomes the log of 1, which is equal to 0. Therefore, when the two components of the buffer system are equal, the pH of the solution is the same as the pK (6.1) of the bicarbonate buffer system. When base is added to the system, part of the dissolved CO_2 is converted into HCO_3^-, causing an increase in the ratio of HCO_3^- to CO_2 and increasing the pH, as is evident from the Henderson-Hasselbalch equation. When acid is added, it is buffered by HCO_3^-, which is then converted into dissolved CO_2, decreasing the ratio of HCO_3^- to CO_2 and decreasing the pH of the extracellular fluid.

Buffer Power Determined by Amount and Relative Concentrations of Buffer Components. From the titration curve in Figure 31-1, several points are apparent. First, the pH of the system is the same as the pK when each of the components (HCO_3^- and CO_2) constitutes 50% of the total concentration of the buffer system. Second, the buffer system is most effective in the central part of

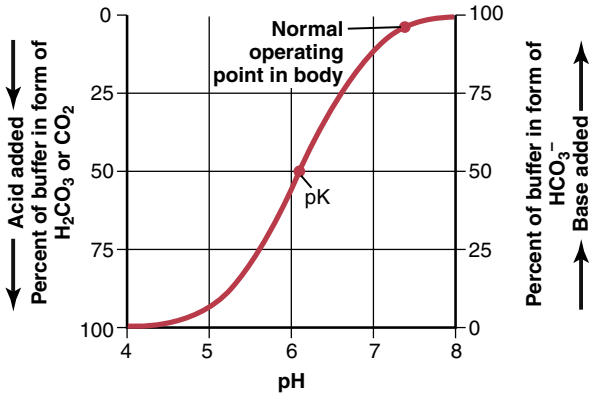


Figure 31-1. Titration curve for bicarbonate buffer system showing the pH of extracellular fluid when the percentages of buffer in the form of HCO_3^- and CO_2 (or H_2CO_3) are altered.

the curve, where the pH is near the pK of the system. This phenomenon means that the change in pH for any given amount of acid or base added to the system is least when the pH is near the pK of the system. The buffer system is still reasonably effective for 1.0 pH unit on either side of the pK, which, for the bicarbonate buffer system, extends from a pH of about 5.1 to 7.1 units. Beyond these limits, the buffering power rapidly diminishes. And, when all the CO_2 has been converted into HCO_3^-, or when all the HCO_3^- has been converted into CO_2, the system has no more buffering power.

The absolute concentration of the buffers is also an important factor in determining the buffer power of a system. With low concentrations of the buffers, only a small amount of acid or base added to the solution changes the pH considerably.

Bicarbonate Buffer System Is the Most Important Extracellular Buffer. From the titration curve shown in Figure 31-1, one would not expect the bicarbonate buffer system to be powerful, for two reasons. First, the pH of the extracellular fluid is about 7.4, whereas the pK of the bicarbonate buffer system is 6.1, which means that there is about 20 times as much of the bicarbonate buffer system in the form of HCO_3^- as in the form of dissolved CO_2. For this reason, this system operates on the portion of the buffering curve where the slope is low, and the buffering power is poor. Second, the concentrations of the two elements of the bicarbonate system, CO_2 and HCO_3^-, are not high.

Despite these characteristics, the bicarbonate buffer system is the most powerful extracellular buffer in the body. This apparent paradox is due mainly to the fact that the two elements of the buffer system, HCO_3^- and CO_2, are regulated, respectively, by the kidneys and lungs, as discussed later. As a result of this regulation, the pH of the extracellular fluid can be precisely controlled by the relative rate of removal and addition of HCO_3^- by the kidneys and rate of removal of CO_2 by the lungs.

PHOSPHATE BUFFER SYSTEM

Although the phosphate buffer system is not a major extracellular fluid buffer, it plays an important role in buffering renal tubular fluid and intracellular fluids.

The main elements of the phosphate buffer system are $H_2PO_4^-$ and $HPO_4^=$. When a strong acid such as HCl is added to a mixture of these two substances, the hydrogen is accepted by the base $HPO_4^=$ and converted to $H_2PO_4^-$:

$$HCl + Na_2HPO_4 \rightarrow NaH_2PO_4 + NaCl$$

The result of this reaction is that the strong acid, HCl, is replaced by an additional amount of a weak acid, NaH_2PO_4, and the decrease in pH is minimized.

When a strong base, such as NaOH, is added to the buffer system, the OH^- is buffered by the $H_2PO_4^-$ to form additional amounts of $HPO_4^=$ + H_2O:

$$NaOH + NaH_2PO_4 \rightarrow Na_2HPO_4 + H_2O$$

In this case, a strong base, NaOH, is traded for a weak base, Na_2HPO_4, causing only a slight increase in pH.

The phosphate buffer system has a pK of 6.8, which is not far from the normal pH of 7.4 in the body fluids, allows the system to operate near its maximum buffering power. However, its concentration in the extracellular fluid is low, at only about 8% of the concentration of the bicarbonate buffer. Therefore, the total buffering power of the phosphate system in the extracellular fluid is much less than that of the bicarbonate buffering system.

In contrast to its minor role as an extracellular buffer, *the phosphate buffer is especially important in the tubular fluids of the kidneys* for two reasons: (1) phosphate usually becomes greatly concentrated in the tubules, thereby increasing the buffering power of the phosphate system; and (2) the tubular fluid usually has a considerably lower pH than the extracellular fluid, bringing the operating range of the buffer closer to the pK (6.8) of the system.

The phosphate buffer system is also important in buffering intracellular fluid because the concentration of phosphate in this fluid is many times higher than in the extracellular fluid. Also, the pH of intracellular fluid is lower than that of extracellular fluid and, therefore, is usually closer to the pK of the phosphate buffer system compared with the extracellular fluid.

PROTEINS ARE IMPORTANT INTRACELLULAR BUFFERS

Proteins are among the most plentiful buffers in the body because of their high concentrations, especially in the cells. The pH of the cells, although slightly lower than in the extracellular fluid, nevertheless changes approximately in proportion to extracellular fluid pH changes. There is a slight diffusion of H^+ and HCO_3^- through the cell membrane, although these ions require several hours to reach equilibrium with the extracellular fluid, except for the rapid equilibrium that occurs in the red blood cells. CO_2, however, can rapidly diffuse through all the cell membranes. *This diffusion of the elements of the bicarbonate buffer system causes the pH in intracellular fluid to change when there are changes in extracellular pH.* For this reason, the buffer systems in the cells help prevent changes in the pH of the extracellular fluid but may take several hours to become maximally effective.

In the red blood cell, hemoglobin (Hb) is an important buffer, as follows:

$$H^+ + Hb \rightleftharpoons HHb$$

Approximately 60% to 70% of the total chemical buffering of the body fluids is inside the cells, and most of this buffering results from the intracellular proteins. However, except for the red blood cells, the slow rate at which H^+ and HCO_3^- move through the cell membranes often delays the maximum ability of the intracellular proteins to buffer extracellular acid–base abnormalities for several hours.

In addition to the high concentration of proteins in the cells, another factor that contributes to their buffering power is the fact that the pKs of many of these protein systems are fairly close to intracellular pH.

Isohydric Principle: All Buffers in a Common Solution Are in Equilibrium With the Same H^+ Concentration

We have been discussing buffer systems as though they operate individually in the body fluids. However, they all work together because H^+ is common to the reactions of all these systems. Therefore, whenever there is a change in H^+ concentration in the extracellular fluid, the balance of all the buffer systems changes at the same time. This phenomenon is called the *isohydric principle* and is illustrated by the following formula:

$$H^+ = K_1 \times \frac{HA_1}{A_1} = K_2 \times \frac{HA_2}{A_2} = K_3 \times \frac{HA_3}{A_3}$$

K_1, K_2, and K_3 are the dissociation constants of three respective acids—HA_1, HA_2, HA_3—and A_1, A_2, A_3 are the concentrations of the free negative ions that constitute the bases of the three buffer systems.

The implication of this principle is that any condition that changes the balance of one of the buffer systems also changes the balance of all the others because the buffer systems actually buffer one another by shifting H^+ back and forth between them.

RESPIRATORY REGULATION OF ACID–BASE BALANCE

The second line of defense against acid–base disturbances is control of extracellular fluid CO_2 concentration by the lungs. An increase in ventilation eliminates CO_2 from extracellular fluid, which, by mass action, reduces the H^+ concentration. Conversely, decreased ventilation increases CO_2 and H^+ concentrations in the extracellular fluid.

PULMONARY EXPIRATION OF CO_2 BALANCES METABOLIC FORMATION OF CO_2

CO_2 is formed continually in the body by intracellular metabolic processes. After it is formed, it diffuses from the cells into the interstitial fluids and blood, and the flowing blood transports it to the lungs, where it diffuses into the alveoli and then is transferred to the atmosphere by pulmonary ventilation. About 1.2 mol/L of dissolved CO_2 is normally in the extracellular fluid, corresponding to a P_{CO_2} of 40 mm Hg.

If the rate of metabolic formation of CO_2 increases, the P_{CO_2} of the extracellular fluid is likewise increased. Conversely, a decreased metabolic rate lowers the P_{CO_2}. If the rate of pulmonary ventilation is increased, CO_2 is blown off from the lungs, and the P_{CO_2} in the extracellular fluid decreases. Therefore, changes in pulmonary ventilation or the rate of CO_2 formation by the tissues can change the extracellular fluid P_{CO_2}.

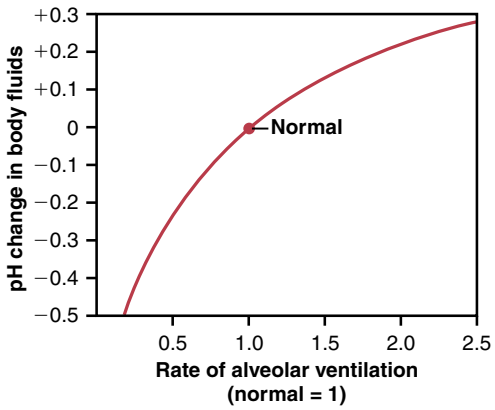


Figure 31-2. Change in extracellular fluid pH caused by an increased or decreased rate of alveolar ventilation, expressed as times normal.

INCREASING ALVEOLAR VENTILATION DECREASES EXTRACELLULAR FLUID H^+ CONCENTRATION AND RAISES PH

If the metabolic formation of CO_2 remains constant, the only other factor that affects P_{CO_2} in extracellular fluid is the rate of alveolar ventilation. The higher the alveolar ventilation, the lower the P_{CO_2}. As discussed previously, when CO_2 concentration increases, the H_2CO_3 concentration and H^+ concentration also increase, thereby lowering extracellular fluid pH.

Figure 31-2 shows the approximate changes in blood pH that are caused by increasing or decreasing the alveolar ventilation rate. Note that increasing alveolar ventilation to about twice normal raises extracellular fluid pH by about 0.23. If the pH of the body fluids is 7.40 with normal alveolar ventilation, doubling the ventilation rate raises the pH to about 7.63. Conversely, a decrease in alveolar ventilation to one-fourth normal reduces the pH by 0.45. That is, if the pH is 7.4 at a normal alveolar ventilation, reducing the ventilation to one-fourth normal reduces the pH to 6.95. Because the alveolar ventilation rate can change markedly, from as low as 0 to as high as 15 times normal, one can easily understand how much the pH of the body fluids can be changed by the respiratory system.

INCREASED H^+ CONCENTRATION STIMULATES ALVEOLAR VENTILATION

Not only does the alveolar ventilation rate influence H^+ concentration by changing P_{CO_2} of the body fluids, but the H^+ concentration affects the rate of alveolar ventilation. Thus, Figure 31-3 shows that alveolar ventilation rate increases four to five times normal as pH decreases from the normal value of 7.4 to the strongly acidic value of 7.0. Conversely, a rise in plasma pH above 7.4 causes a decrease in the ventilation rate. The change in ventilation rate per unit pH change is much greater at reduced levels of pH (corresponding to elevated H^+ concentration) compared with increased levels of pH. The reason for this is that as the

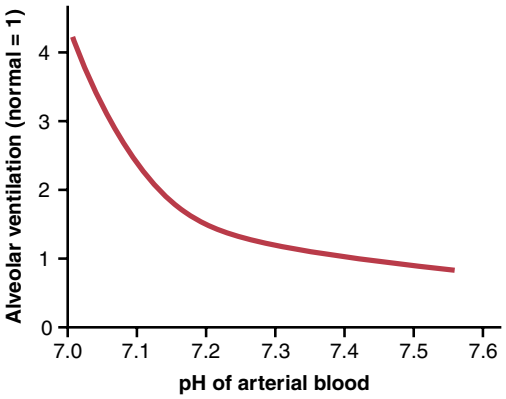
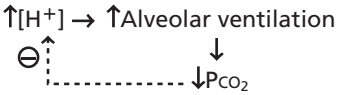


Figure 31-3. Effect of blood pH on the alveolar ventilation rate.

alveolar ventilation rate decreases, as a result of an increase in pH (decreased H^+ concentration), the amount of oxygen added to the blood decreases, and the partial pressure of oxygen (P_{O_2}) in the blood also decreases, which stimulates the ventilation rate. Therefore, the respiratory compensation for an increase in pH is not nearly as effective as the response to a marked reduction in pH.

Feedback Control of H^+ Concentration by the Respiratory System. Because increased H^+ concentration stimulates respiration and because increased alveolar ventilation decreases H^+ concentration, the respiratory system acts as a typical negative feedback controller of H^+ concentration:



That is, whenever H^+ concentration increases above normal, the respiratory system is stimulated, and alveolar ventilation increases. This mechanism decreases the P_{CO_2} in extracellular fluid and reduces H^+ concentration back toward normal. Conversely, if H^+ concentration falls below normal, the respiratory center becomes depressed, alveolar ventilation decreases, and H^+ concentration increases back toward normal. Although alkalosis tends to depress the respiratory centers, the response is generally less robust and less predictable than the response to metabolic acidosis; the hypoxemia associated with reduced alveolar ventilation eventually activates oxygen-sensitive chemoreceptors that tend to stimulate ventilation and limit the respiratory compensation for metabolic alkalosis.

Efficiency of Respiratory Control of H^+ Concentration. Respiratory control cannot return the H^+ concentration all the way back to normal when a disturbance outside the respiratory system has altered the pH. Ordinarily, the respiratory mechanism for controlling H^+ concentration is approximately 50% to 75% effective, corresponding to a *feedback gain* of 1 to 3 for metabolic acidosis. That is, if the pH is suddenly decreased by adding acid to the extracellular fluid, and the pH falls from 7.4 to 7.0, the respiratory system can return the pH to a value of about 7.2 to 7.3. This response occurs within 3 to 12 minutes. As discussed previously, the respiratory responses to metabolic alkalosis are limited by hypoxemia associated with reduced alveolar ventilation.

Buffering Power of the Respiratory System. *Respiratory regulation of acid–base balance is a physiological type of buffer system* because it acts rapidly and keeps the H^+ concentration from changing too much until the slowly responding kidneys can eliminate the imbalance. In general, the overall buffering power of the respiratory system is one to two times as great as the buffering power of all other chemical buffers in the extracellular fluid combined. That is, one to two times as much acid or base can normally be buffered by this mechanism as by the chemical buffers.

Impairment of Lung Function Can Cause Respiratory Acidosis. We have discussed thus far the role of the *normal* respiratory mechanism as a means of buffering changes in H^+ concentration. However, *abnormalities of respiration* can also cause changes in H^+ concentration. For example, an impairment of lung function, such as severe emphysema, decreases the ability of the lungs to eliminate CO_2, which causes a buildup of CO_2 in the extracellular fluid and a tendency toward *respiratory acidosis*. Also, the ability to respond to metabolic acidosis is impaired because the compensatory reductions in P_{CO_2} that would normally occur by means of increased ventilation are blunted. In these circumstances, the kidneys represent the sole remaining physiological mechanism for returning pH toward normal after the initial chemical buffering in the extracellular fluid has occurred.

RENAL CONTROL OF ACID–BASE BALANCE

The kidneys control acid–base balance by excreting acidic or basic urine. Excreting acidic urine reduces the amount of acid in extracellular fluid, whereas excreting basic urine removes base from the extracellular fluid.

The overall mechanism whereby the kidneys excrete acidic or basic urine is as follows. Large amounts of HCO_3^- are filtered continuously into the tubules and, if excreted into the urine, remove base from the blood. Large numbers of H^+ are also secreted into the tubular lumen by the tubular epithelial cells, thus removing acid from the blood. If more H^+ is secreted than HCO_3^- is filtered, there will be a net loss of acid from the extracellular fluid. Conversely, if more HCO_3^- is filtered than H^+ is secreted, there will be a net loss of base.

Each day, the body produces about 80 mEq of nonvolatile acids, mainly from metabolism of proteins. These acids are called *nonvolatile* because they are not H_2CO_3 and,

therefore, cannot be excreted by the lungs. The primary mechanism for removal of these acids from the body is renal excretion. The kidneys must also prevent the loss of bicarbonate in the urine, a task that is quantitatively more important than the excretion of nonvolatile acids. Each day, the kidneys filter about 4320 mEq of HCO_3^- (180 L/day × 24 mEq/L); under normal conditions, almost all of this is reabsorbed from the tubules, thereby conserving the primary buffer system of the extracellular fluid.

As discussed later, both the reabsorption of HCO_3^- and excretion of H^+ are accomplished through the process of H^+ secretion by the tubules. Because HCO_3^- must react with a secreted H^+ to form H_2CO_3 before it can be reabsorbed, 4320 mEq of H^+ must be secreted each day just to reabsorb the filtered HCO_3^-. Then, an additional 80 mEq of H^+ must be secreted to rid the body of the nonvolatile acids produced each day for a total of 4400 mEq of H^+ secreted into the tubular fluid each day.

When there is a reduction in the extracellular fluid H^+ concentration (alkalosis), the kidneys usually secrete less H^+ and fail to reabsorb all the filtered HCO_3^-, thereby increasing the excretion of HCO_3^-. Because HCO_3^- normally buffers H^+ in the extracellular fluid, this loss of HCO_3^- is the same as adding an H^+ to the extracellular fluid. Therefore, in alkalosis, the removal of HCO_3^- raises the extracellular fluid H^+ concentration back toward normal.

In acidosis, the kidneys secrete additional H^+ and do not excrete HCO_3^- into the urine but reabsorb all the filtered HCO_3^- and produce new HCO_3^-, which is added back to the extracellular fluid. This action reduces the extracellular fluid H^+ concentration back toward normal.

Thus, the kidneys regulate extracellular fluid H^+ concentration through three fundamental mechanisms: (1) secretion of H^+; (2) reabsorption of filtered HCO_3^-; and (3) production of new HCO_3^-. All these processes are accomplished through the same basic mechanisms, as discussed in the next few sections.

SECRETION OF H^+ AND REABSORPTION OF HCO_3^- BY THE RENAL TUBULES

Hydrogen ion secretion and HCO_3^- reabsorption occur in virtually all parts of the tubules except the descending and ascending thin limbs of the loop of Henle. **Figure 31-4** summarizes HCO_3^- reabsorption along the tubule. Keep in mind that for *each HCO_3^- reabsorbed, an H^+ must be secreted.*

About 80% to 90% of the HCO_3^- reabsorption (and H^+ secretion) occurs in the proximal tubule, so only a small amount of HCO_3^- flows into the distal tubules and collecting ducts. In the thick ascending loop of Henle, another 10% of the filtered HCO_3^- is reabsorbed, and the remainder of the reabsorption takes place in the distal tubules and collecting ducts. As discussed previously, the mechanism whereby HCO_3^- is reabsorbed also involves tubular secretion of H^+, but different tubular segments accomplish this task differently.

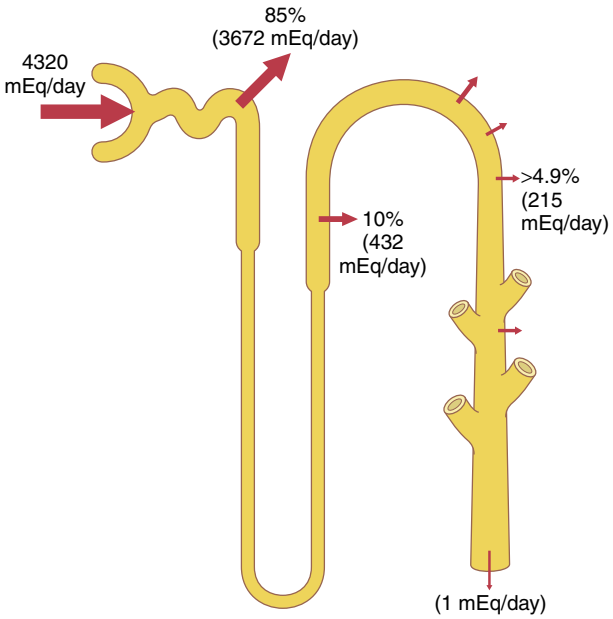


Figure 31-4. Reabsorption of HCO_3^- in different segments of the renal tubule. The percentages of the filtered load of HCO_3^- absorbed by the various tubular segments are shown, as well as the number of milliequivalents reabsorbed per day under normal conditions.

H^+ SECRETED BY SECONDARY ACTIVE TRANSPORT IN EARLY TUBULAR SEGMENTS

The epithelial cells of the proximal tubule, the thick segment of the ascending loop of Henle, and the early distal tubule all secrete H^+ into the tubular fluid by sodium-hydrogen counter-transport, as shown in **Figure 31-5**. This secondary active secretion of H^+ is coupled with the transport of Na^+ into the cell at the luminal membrane by the *sodium-hydrogen exchanger protein*, and the energy for H^+ secretion against a concentration gradient is derived from the sodium gradient favoring Na^+ movement into the cell. This gradient is established by the sodium-potassium adenosine triphosphatase (Na^+-K^+ ATPase) pump in the basolateral membrane. About 95% of the bicarbonate is reabsorbed in this manner, requiring about 4000 mEq of H^+ to be secreted each day by the tubules. This mechanism, however, can establish a minimum pH of only about 6.7; the tubular fluid becomes very acidic only in the collecting tubules and collecting ducts, which can establish a urine pH as low as about 4.5.

Figure 31-5 shows how the process of H^+ secretion achieves HCO_3^- reabsorption. The secretory process begins when CO_2 either diffuses into the tubular cells or is formed by metabolism in the tubular epithelial cells. Under the influence of the enzyme *carbonic anhydrase*, CO_2, combines with H_2O to form H_2CO_3, which dissociates into HCO_3^- and H^+. The H^+ is secreted from the cell into the tubular lumen by sodium-hydrogen counter-transport. That is, when Na^+ moves from the lumen of the tubule to the interior of the cell, it first combines with a

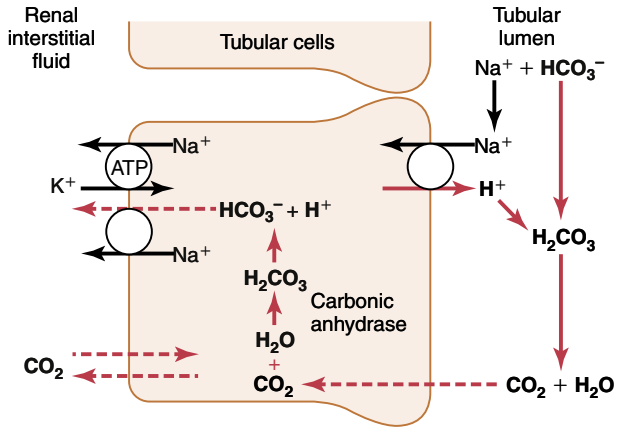


Figure 31-5. Shown are the cellular mechanisms for the following: (1) active secretion of H^+ into the renal tubule; (2) tubular reabsorption of HCO_3^- by combination with H^+ to form H_2CO_3, which dissociates to form CO_2 and H_2O; and (3) Na^+ reabsorption in exchange for H^+ secreted. This pattern of H^+ secretion occurs in the proximal tubule, thick ascending segment of the loop of Henle, and early distal tubule.

carrier protein in the luminal border of the cell membrane; at the same time, a H^+ in the interior of the cells combines with the carrier protein. The Na^+ moves into the cell down a concentration gradient that has been established by the Na^+-K^+ ATPase pump in the basolateral membrane. The gradient for Na^+ movement into the cell then provides the energy for moving H^+ in the opposite direction from the interior of the cell to the tubular lumen.

The HCO_3^- generated in the cell (when H^+ dissociates from H_2CO_3) then moves downhill across the basolateral membrane, into the renal interstitial fluid and peritubular capillary blood. The net result is that for every H^+ secreted into the tubular lumen, an HCO_3^- enters the blood.

FILTERED HCO_3^- IS REABSORBED BY INTERACTION WITH H^+ IN THE TUBULES

Bicarbonate ions do not readily permeate the luminal membranes of the renal tubular cells; therefore, HCO_3^- that is filtered by the glomerulus cannot be directly reabsorbed. Instead, HCO_3^- is reabsorbed by a special process in which it first combines with H^+ to form H_2CO_3, which eventually becomes CO_2 and H_2O, as shown in **Figure 31-5**.

This reabsorption of HCO_3^- is initiated by a reaction in the tubules between HCO_3^- filtered at the glomerulus and H^+ secreted by the tubular cells. The H_2CO_3 formed then dissociates into CO_2 and H_2O. The CO_2 can move easily across the tubular membrane; therefore, it instantly diffuses into the tubular cell, where it recombines with H_2O, under the influence of carbonic anhydrase, to generate a new H_2CO_3 molecule. This H_2CO_3 dissociates to form HCO_3^- and H^+; the HCO_3^- then diffuses through the basolateral membrane into the interstitial fluid and is taken up into the peritubular capillary blood. The transport of HCO_3 across the basolateral membrane is facilitated by two mechanisms: (1) Na^+-HCO_3^- co-transport in the proximal tubules; and (2) Cl^--HCO_3^- exchange in the late segments of the proximal tubule, thick ascending loop of Henle, and collecting tubules and ducts.

Thus, each time a H^+ is formed in the tubular epithelial cells, an HCO_3^- is also formed and released back into the blood. The net effect of these reactions is "reabsorption" of HCO_3^- from the tubules, although the HCO_3^- that actually enters the extracellular fluid is not the same as that filtered into the tubules. The reabsorption of filtered HCO_3^- does not result in net secretion of H^+ because the secreted H^+ combines with the filtered HCO_3^- and is therefore not excreted.

HCO_3^- Is Titrated Against H^+ in the Tubules. Under normal conditions, the rate of tubular H^+ secretion is about 4400 mEq/day, and the rate of filtration by HCO_3^- is about 4320 mEq/day. Thus, the quantities of these two ions entering the tubules are almost equal, and they combine with each other to form CO_2 and H_2O. Therefore, it is said that HCO_3^- and H^+ normally "titrate" each other in the tubules.

The titration process is not quite exact because there is usually a slight excess of H^+ in the tubules to be excreted in the urine. This excess H^+ (≈80 mEq/day) rids the body of nonvolatile acids produced by metabolism. As discussed later, most of this H^+ is not excreted as free H^+ but is in combination with other urinary buffers, especially phosphate and ammonia.

When there is an excess of HCO_3^- over H^+ in the urine, as occurs in metabolic alkalosis, the excess HCO_3^- cannot be reabsorbed. Therefore, the excess HCO_3^- is left in the tubules and eventually excreted into the urine, which helps correct the metabolic alkalosis.

In acidosis, there is excess H^+ relative to HCO_3^-, causing complete reabsorption of the HCO_3^-; the excess H^+ passes into the urine in combination with urinary buffers, especially phosphate and ammonia, and eventually is excreted as salts. Thus, the basic mechanism whereby the kidneys correct acidosis or alkalosis is incomplete titration of H^+ against HCO_3^-, leaving one or the other to pass into the urine and be removed from the extracellular fluid.

PRIMARY ACTIVE SECRETION OF H^+ IN THE INTERCALATED CELLS OF LATE DISTAL AND COLLECTING TUBULES

Beginning in the late distal tubules and continuing through the remainder of the tubular system, the tubular epithelium secretes H^+ by *primary active transport*. The characteristics of this transport are different from those discussed for the proximal tubule, loop of Henle, and early distal tubule.

The mechanism for primary active H^+ secretion was discussed in Chapter 28 and is shown in **Figure 31-6**. It occurs at the luminal membrane of the tubular cell, where H^+ is transported directly by specific proteins, a *hydrogen-transporting ATPase* and a *hydrogen-potassium-ATPase transporter*. The energy required for pumping the H^+ is derived from the breakdown of ATP to adenosine diphosphate.

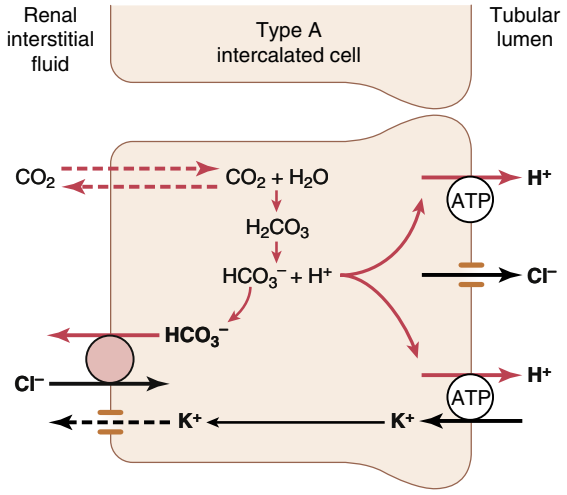


Figure 31-6. Active secretion of H^+ through the luminal membrane of the type A intercalated epithelial cells of the late distal and collecting tubules. Type A cells contain hydrogen–adenosine triphosphatase (ATPase) and hydrogen-potassium-ATPase in the luminal membrane and secrete H^+ while reabsorbing HCO_3^- and K^+ in acidosis. Note that one HCO_3^- is reabsorbed for each H^+ secreted, and one Cl^- is passively secreted along with H^+.

Primary active secretion of H^+ occurs in special types of cells called the *type A intercalated cells* of the late distal tubule and in the collecting tubules. Hydrogen ion secretion in these cells is accomplished in two steps: (1) the dissolved CO_2 in this cell combines with H_2O to form H_2CO_3; and (2) the H_2CO_3 then dissociates into HCO_3^-, which is reabsorbed into the blood, plus H^+, which is secreted into the tubule by means of the hydrogen-ATPase and the hydrogen-potassium-ATPase transporters. For each H^+ secreted, a HCO_3^- is reabsorbed, similar to the process in the proximal tubules. The main difference is that H^+ moves across the luminal membrane by an active H^+ pump instead of by counter-transport, as occurs in the early parts of the nephron.

Although secretion of H^+ in the late distal tubule and collecting tubules accounts for only about 5% of the total H^+ secreted, this mechanism is important in forming maximally acidic urine. In the proximal tubules, H^+ concentration can be increased only about threefold to fourfold and the tubular fluid pH can be reduced to only about 6.7, although large *amounts* of H^+ are secreted by this nephron segment. However, H^+ concentration can be increased as much as 900-fold in the collecting tubules. This mechanism decreases the pH of the tubular fluid to about 4.5, which is the lower limit of pH that can be achieved in normal kidneys.

COMBINATION OF EXCESS H^+ WITH PHOSPHATE AND AMMONIA BUFFERS IN THE TUBULE GENERATES "NEW" HCO_3^-

When H^+ is secreted in excess of the HCO_3^- filtered into the tubular fluid, only a small part of the excess H^+ can be excreted in the ionic form (H^+) in the urine. This is because the minimal urine pH is about 4.5, corresponding to an H^+ concentration of $10^{-4.5}$ mEq/L, or 0.03 mEq/L. Thus, for each liter of urine formed, a maximum of only about 0.03 mEq of free H^+ can be excreted. To excrete the 80 mEq of nonvolatile acid formed by metabolism each day, about 2667 liters of urine would have to be excreted if the H^+ remained free in solution.

The excretion of large amounts of H^+ (on occasion as much as 500 mEq/day) in the urine is accomplished primarily by combining the H^+ with buffers in the tubular fluid. The most important buffers are phosphate buffer and ammonia buffer. Other weak buffer systems, such as urate and citrate, are much less important.

When H^+ is titrated in the tubular fluid with HCO_3^-, this leads to reabsorption of one HCO_3^- for each H^+ secreted, as discussed earlier. However, when there is excess H^+ in the tubular fluid, it combines with buffers other than HCO_3^-, and this leads to generation of new HCO_3^- that can also enter the blood. Thus, when there is excess H^+ in the extracellular fluid, the kidneys not only reabsorb all the filtered HCO_3^- but also generate new HCO_3^-, thereby helping replenish the HCO_3^- lost from the extracellular fluid in acidosis. In the next two sections, we discuss the mechanisms whereby phosphate and ammonia buffers contribute to generation of new HCO_3^-.

PHOSPHATE BUFFER SYSTEM CARRIES EXCESS H^+ INTO THE URINE AND GENERATES NEW HCO_3^-

The phosphate buffer system is composed of $HPO_4^=$. Both become concentrated in the tubular fluid because water is normally reabsorbed to a greater extent than phosphate by the renal tubules. Therefore, although phosphate is not an important extracellular fluid buffer, it is much more effective as a buffer in the tubular fluid.

Another factor that makes phosphate important as a tubular buffer is the fact that the pK of this system is about 6.8. Under normal conditions, the urine is slightly acidic, and the urine pH is near the pK of the phosphate buffer system. Therefore, in the tubules, the phosphate buffer system normally functions near its most effective pH range.

Figure 31-7 shows the sequence of events whereby H^+ is excreted in combination with phosphate buffer and the mechanism whereby new HCO_3^- is added to the blood. The process of H^+ secretion into the tubules is the same as described earlier. As long as there is excess HCO_3^- in the tubular fluid, most of the secreted H^+ combines with HCO_3^-. However, once all the HCO_3^- has been reabsorbed and is no longer available to combine with H^+, any excess H^+ can combine with $HPO_4^=$ and other tubular buffers. After the H^+ combines with $HPO_4^=$ to form $H_2PO_4^-$, it can be excreted as a sodium salt (NaH_2PO_4), carrying with it the excess H^+.

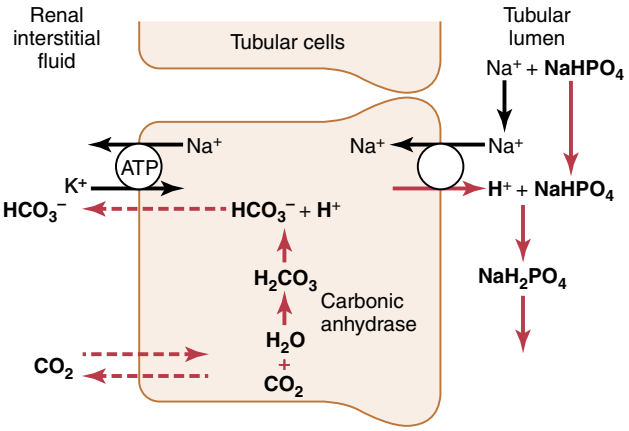


Figure 31-7. Buffering of secreted H^+ by filtered phosphate ($NaHPO_4$). Note that a new HCO_3^- is returned to the blood for each $NaHPO_4$ that reacts with a secreted H^+.

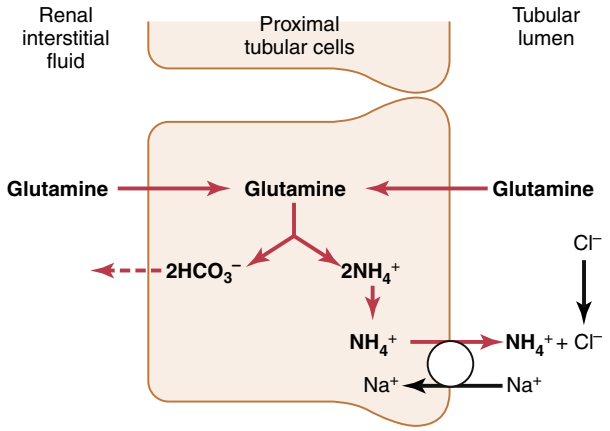


Figure 31-8. Production and secretion of ammonium ion (NH_4^+) by proximal tubular cells. Glutamine is metabolized in the cell, yielding NH_4^+ and HCO_3^-. The NH_4^+ is secreted into the lumen by a Na^+-NH_4^+ exchanger. For each glutamine molecule metabolized, two NH_4^+ are produced and secreted, and two HCO_3^- are returned to the blood.

There is one important difference in this sequence of H^+ excretion from that discussed previously. In this case, the HCO_3^- that is generated in the tubular cell and enters the peritubular blood represents a net gain of HCO_3^- by the blood, rather than merely a replacement of filtered HCO_3^-. *Therefore, whenever an H^+ secreted into the tubular lumen combines with a buffer other than HCO_3^-, the net effect is the addition of a new HCO_3^- to the blood.* This process demonstrates one of the mechanisms whereby the kidneys can replenish the extracellular fluid stores of HCO_3^-.

Under normal conditions, much of the filtered phosphate is reabsorbed, and only 30 to 40 mEq/day are available for buffering H^+. Therefore, much of the buffering of excess H^+ in the tubular fluid in acidosis occurs through the ammonia buffer system.

EXCRETION OF EXCESS H^+ AND GENERATION OF NEW HCO_3^- BY AMMONIA BUFFER SYSTEM

A second buffer system in the tubular fluid that is even more important quantitatively than the phosphate buffer system is composed of ammonia (NH_3) and the ammonium ion (NH_4^+). Ammonium ion is synthesized from glutamine, which comes mainly from metabolism of amino acids in the liver. The glutamine delivered to the kidneys is transported into epithelial cells of the proximal tubules, thick ascending limb of the loop of Henle, and distal tubules (Figure 31-8). Once inside the cell, each molecule of glutamine is metabolized in a series of reactions to ultimately form two NH_4^+ and two HCO_3^-. The NH_4^+ is secreted into the tubular lumen by a countertransport mechanism in exchange for sodium, which is reabsorbed. The HCO_3^- is transported across the basolateral membrane, along with the reabsorbed Na^+, into the interstitial fluid and is taken up by the peritubular capillaries. Thus, for each molecule of glutamine metabolized in the proximal tubules, two NH_4^+ are secreted into the urine and two HCO_3^- are reabsorbed into the blood. *The HCO_3^- generated by this process constitutes new HCO_3^-.*

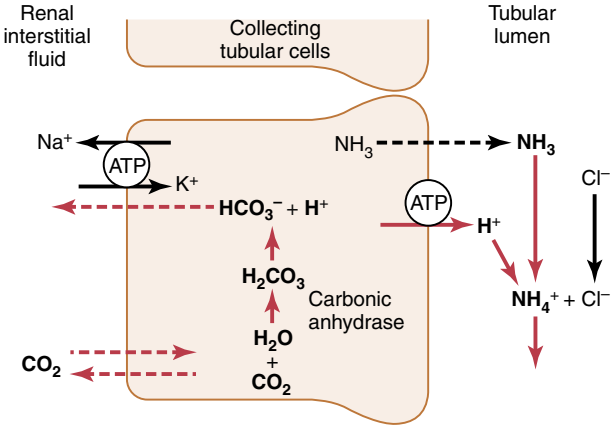


Figure 31-9. Buffering of H^+ secretion by ammonia (NH_3) in the collecting tubules. NH_3 diffuses into the tubular lumen, where it reacts with secreted H^+ to form NH_4^+, which is then excreted. For each NH_4^+ excreted, a new HCO_3^- is formed in the tubular cells and returned to the blood.

In the collecting tubules, the addition of NH_4^+ to the tubular fluids occurs through a different mechanism (Figure 31-9). Here, H^+ is actively secreted by the tubular membrane into the lumen, where it combines with NH_3 to form NH_4^+, which is then excreted. The collecting ducts are permeable to NH_3, which can easily diffuse into the tubular lumen. However, the luminal membrane of this part of the tubules is much less permeable to NH_4^+; therefore, once the H^+ has reacted with NH_3 to form NH_4^+, the NH_4^+ is trapped in the tubular lumen and eliminated in the urine. *For each NH_4^+ excreted, a new HCO_3^- is generated and added to the blood.*

Chronic Acidosis Increases NH_4^+ Excretion. One of the most important features of the renal ammonium-ammonia buffer system is that it is subject to physiological

control. An increase in extracellular fluid H^+ concentration stimulates renal glutamine metabolism and, therefore, increases formation of NH_4^+ and new HCO_3^- to be used in H^+ buffering; a decrease in H^+ concentration has the opposite effect.

Under *normal conditions*, the amount of H^+ eliminated by the ammonia buffer system accounts for about 50% of the acid excreted and 50% of the new HCO_3^- generated by the kidneys. However, with *chronic acidosis*, the rate of NH_4^+ excretion can increase to as much as 500 mEq/day. *Therefore, with chronic acidosis, the dominant mechanism for acid elimination is excretion of NH_4^+.* This process also provides the most important mechanism for generating new bicarbonate during chronic acidosis.

QUANTIFYING RENAL ACID–BASE EXCRETION

Based on the principles discussed earlier, we can quantify the kidneys' net excretion of acid or net addition or elimination of HCO_3^- from the blood as follows.

Bicarbonate excretion is calculated as urine flow rate multiplied by the urinary HCO_3^- concentration and indicates how rapidly the kidneys are removing HCO_3^- from the blood, which is the same as adding an H^+ to the blood. In alkalosis, the loss of HCO_3^- helps return the plasma pH toward normal.

The amount of new HCO_3^- contributed to the blood at any given time is equal to the amount of H^+ secreted that ends up in the tubular lumen with non-bicarbonate urinary buffers. As discussed previously, the primary sources of nonbicarbonate urinary buffers are NH_4^+ and phosphate. Therefore, part of the HCO_3^- added to the blood (and H^+ excreted by NH_4^+) is calculated by measuring NH_4^+ excretion (urine flow rate multiplied by urinary NH_4^+ concentration).

The rest of the non-bicarbonate, non-NH_4^+ buffer excreted in the urine is measured by determining a value known as *titratable acid*. The amount of titratable acid in the urine is measured by titrating the urine with a strong base, such as NaOH, to a pH of 7.4, the pH of normal plasma and the pH of the glomerular filtrate. This titration reverses the events that occurred in the tubular lumen when the tubular fluid was titrated by secreted H^+. Therefore, the number of milliequivalents of NaOH required to return the urinary pH to 7.4 equals the number of milliequivalents of H^+ added to the tubular fluid that combined with phosphate and other organic buffers. The titratable acid measurement does not include H^+ in association with NH_4^+ because the pK of the ammonia-ammonium reaction is 9.2, and titration with NaOH to a pH of 7.4 does not remove the H^+ from NH_4^+.

Thus, the *net acid excretion* by the kidneys can be assessed as follows:

$$\text{Net acid excretion} = NH_4^+ \text{ excretion} + \text{Urinary titratable acid} - HCO_3^- \text{ excretion}$$

The reason we subtract HCO_3^- excretion is that the loss of HCO_3^- is the same as the addition of H^+ to the blood. To maintain acid–base balance, the net acid excretion must equal the nonvolatile acid production in the body.

In acidosis, the net acid excretion increases markedly, especially because of increased NH_4^+ excretion, thereby removing acid from the blood. The net acid excretion also equals the rate of net HCO_3^- addition to the blood. *Therefore, in acidosis, there is a net addition of HCO_3^- back to the blood as more NH_4^+ and urinary titratable acid are excreted.*

In alkalosis, titratable acid and NH_4^+ excretion drop to 0, whereas HCO_3^- excretion increases. *Therefore, in alkalosis, there is a negative net acid secretion,* which means that there is a net loss of HCO_3^- from the blood, which is the same as adding H^+ to the blood, and that no new HCO_3^- is generated by the kidneys.

REGULATION OF RENAL TUBULAR H^+ SECRETION

As discussed earlier, H^+ secretion by the tubular epithelium is necessary for HCO_3^- reabsorption and generation of new HCO_3^- associated with titratable acid formation. Therefore, the rate of H^+ secretion must be carefully regulated if the kidneys are to perform their functions in acid–base homeostasis effectively. Under normal conditions, the kidney tubules must secrete at least enough H^+ to reabsorb almost all the HCO_3^- that is filtered, and there must be enough H^+ left over to be excreted as titratable acid or NH_4^+ to rid the body of the nonvolatile acids produced each day from metabolism.

In alkalosis, the tubular secretion of H^+ is reduced to a level that is too low to achieve complete HCO_3^- reabsorption, enabling the kidneys to increase HCO_3^- excretion. Titratable acid and ammonia are not excreted in alkalosis because there is no excess H^+ available to combine with nonbicarbonate buffers; therefore, no new HCO_3^- is added to the blood in alkalosis.

During acidosis, the tubular H^+ secretion is increased sufficiently to reabsorb all the filtered HCO_3^-, with enough H^+ left over to excrete large amounts of NH_4^+ and titratable acid, thereby contributing large amounts of new HCO_3^- to the total body extracellular fluid. *The most important stimuli for increasing H^+ secretion by the tubules in acidosis are as follows: (1) an increase in P_{CO_2} of the extracellular fluid in respiratory acidosis; and (2) an increase in H^+ concentration of the extracellular fluid (decreased pH) in respiratory or metabolic acidosis.*

The tubular cells respond directly to an increase in P_{CO_2} of the blood, as in respiratory acidosis, with an increase in the rate of H^+ secretion, as follows. The increased P_{CO_2} raises the P_{CO_2} of the tubular cells, causing increased formation of H^+ in the tubular cells, which in turn stimulates secretion of H^+. The second factor that stimulates H^+ secretion is an increase in extracellular fluid H^+ concentration (decreased pH).

Table 31-2 Plasma or Extracellular Fluid Factors That Increase or Decrease H^+ Secretion and HCO_3^- Reabsorption by the Renal Tubules

Increase H^+ Secretion and HCO_3^- Reabsorption	Decrease H^+ Secretion and HCO_3^- Reabsorption
$\uparrow P_{CO_2}$	$\downarrow P_{CO_2}$
$\uparrow H^+$, $\downarrow HCO_3^-$	$\downarrow H^+$, $\uparrow HCO_3^-$
↓Extracellular fluid volume	↑Extracellular fluid volume
↑Angiotensin II	↓Angiotensin II
↑Aldosterone	↓Aldosterone
Hypokalemia	Hyperkalemia

A special factor that can increase H^+ secretion under some pathophysiological conditions is excessive aldosterone secretion. Aldosterone stimulates secretion of H^+ by type A intercalated cells of the collecting tubules and ducts. Therefore, excessive secretion of aldosterone, as in persons with Conn syndrome, increases secretion of H^+ into the tubular fluid and, consequently, increases the amount of HCO_3^- added back to the blood. This action usually causes alkalosis in patients with excessive aldosterone secretion.

The tubular cells usually respond to a decrease in H^+ concentration (alkalosis) by reducing H^+ secretion. The decreased H^+ secretion results from decreased extracellular P_{CO_2}, as in respiratory alkalosis, or from a decrease in H^+ concentration, as in both respiratory and metabolic alkalosis.

Table 31-2 summarizes the major factors that influence H^+ secretion and HCO_3^- reabsorption. Some of these factors are not directly related to the regulation of acid–base balance. For example, H^+ secretion is coupled to Na^+ reabsorption by the Na^+-H^+ exchanger in the proximal tubule and the thick ascending loop of Henle. Therefore, factors that stimulate Na^+ reabsorption, such as decreased extracellular fluid volume and increased angiotensin II (Ang II), may also secondarily increase H^+ secretion and HCO_3^- reabsorption.

Extracellular fluid volume depletion stimulates sodium reabsorption by the renal tubules and increases H^+ secretion and HCO_3^- reabsorption through multiple mechanisms, including the following: (1) increased Ang II levels, which directly stimulate activity of the Na^+-H^+ exchanger in the renal tubules; and (2) increased aldosterone levels, which stimulate H^+ secretion by the intercalated cells of the cortical collecting tubules. Therefore, extracellular fluid volume depletion tends to cause alkalosis due to excess H^+ secretion and HCO_3^- reabsorption.

Changes in plasma potassium concentration can also influence H^+ secretion, with hypokalemia stimulating and hyperkalemia inhibiting H^+ secretion in the proximal tubule. Decreased plasma potassium concentration tends to increase H^+ concentration in the renal tubular cells. This, in turn, stimulates H^+ secretion and HCO_3^- reabsorption and leads to alkalosis. Hyperkalemia decreases H^+ secretion and HCO_3^- reabsorption and tends to cause acidosis.

RENAL CORRECTION OF ACIDOSIS—INCREASED EXCRETION OF H^+ AND ADDITION OF HCO_3^- TO THE EXTRACELLULAR FLUID

Now that we have described the mechanisms whereby the kidneys secrete H^+ and reabsorb HCO_3^-, we can explain how the kidneys readjust the pH of the extracellular fluid when it becomes abnormal.

Referring to Equation 8, the Henderson-Hasselbalch equation, we can see that acidosis occurs when the ratio of HCO_3^- to CO_2 in the extracellular fluid decreases, thereby decreasing the pH. If this ratio decreases because of a fall in HCO_3^-, the acidosis is referred to as *metabolic acidosis.* If the pH falls because of an increase in P_{CO_2}, the acidosis is referred to as *respiratory acidosis*.

ACIDOSIS DECREASES HCO_3^-/H^+ RATIO IN RENAL TUBULAR FLUID

Respiratory and metabolic acidosis both cause a decrease in the ratio of HCO_3^-/H^+ in the renal tubular fluid. As a result, there is excess H^+ in the renal tubules, causing complete reabsorption of HCO_3^- and still leaving additional H^+ available to combine with the urinary buffers NH_4^+ and $HPO_4^=$. Thus, in acidosis, the kidneys reabsorb all the filtered HCO_3^- and contribute new HCO_3^- through formation of NH_4^+ and titratable acid.

In metabolic acidosis, an excess of H^+ over HCO_3^- occurs in the tubular fluid, primarily because of decreased extracellular fluid concentration of HCO_3^- and therefore decreased glomerular filtration of HCO_3^-.

In respiratory acidosis, the excess H^+ in the tubular fluid is due mainly to the rise in extracellular fluid P_{CO_2}, which stimulates H^+ secretion.

As discussed previously, with chronic acidosis, regardless of whether it is respiratory or metabolic, there is increased production of NH_4^+, which further contributes to excretion of H^+ and addition of new HCO_3^- to the extracellular fluid. With severe chronic acidosis, as much as 500 mEq/day of H^+ can be excreted in the urine, mainly in the form of NH_4^+; this excretion, in turn, contributes up to 500 mEq/day of new HCO_3^- that is added to the blood.

Thus, with chronic acidosis, increased secretion of H^+ by the tubules helps eliminate excess H^+ from the body and increases the quantity of HCO_3^- in the extracellular fluid. This process increases the HCO_3^- part of the bicarbonate buffer system, which, in accordance with the Henderson-Hasselbalch equation, helps raise the extracellular pH and corrects the acidosis. If the acidosis is metabolically mediated, additional compensation by the lungs causes a reduction in P_{CO_2}, also helping correct the acidosis.

Table 31-3 Extracellular Fluid Characteristics of Primary Acid–Base Disturbances[a]

	pH	H^+	P_{CO_2}	HCO_3^-
Normal	7.4	40 mEq/L	40 mm Hg	24 mEq/L
Respiratory acidosis	↓	↑	↑↑	↑
Respiratory alkalosis	↑	↓	↓↓	↓
Metabolic acidosis	↓	↑	↓	↓↓
Metabolic alkalosis	↑	↓	↑	↑↑

[a]The primary event is indicated by the double arrows (↑↑ or ↓↓). Note that respiratory acid–base disorders are initiated by an increase or decrease in P_{CO_2}, whereas metabolic disorders are initiated by an increase or decrease in HCO_3^-.

Table 31-3 summarizes the extracellular fluid characteristics associated with respiratory and metabolic acidosis, as well as respiratory and metabolic alkalosis, discussed in the next section. Note that in *respiratory acidosis*, there is a reduction in pH, an increase in extracellular fluid H^+ concentration, and an increase in P_{CO_2}, which is the initial cause of the acidosis. *The compensatory response is increase in plasma HCO_3^-, caused by the addition of new HCO_3^- to the extracellular fluid by the kidneys.* The rise in HCO_3^- helps offset the increase in P_{CO_2}, thereby returning the plasma pH toward normal.

In *metabolic acidosis*, there is also a decrease in pH and a rise in the extracellular fluid H^+ concentration. However, in this case, the primary abnormality is a decrease in plasma HCO_3^-. *The primary compensations include increased ventilation rate, which reduces P_{CO_2}, and renal compensation, which, by adding new HCO_3^- to the extracellular fluid, helps minimize the initial fall in extracellular HCO_3^- concentration.*

RENAL CORRECTION OF ALKALOSIS—DECREASED TUBULAR SECRETION OF H^+ AND INCREASED EXCRETION OF HCO_3^-

The compensatory responses to alkalosis are basically opposite to those that occur in acidosis. In alkalosis, the ratio of HCO_3^- to CO_2 in the extracellular fluid increases, causing a rise in pH (a decrease in H^+ concentration), as evident from the Henderson-Hasselbalch equation.

ALKALOSIS INCREASES HCO_3^-/H^+ RATIO IN RENAL TUBULAR FLUID

Regardless of whether alkalosis is caused by metabolic or respiratory abnormalities, there is still an increase in the ratio of HCO_3^-/H^+ in the renal tubular fluid. The net effect of this is an excess of HCO_3^- that cannot be reabsorbed from the tubules and is, therefore, excreted in the urine. Thus, in alkalosis, HCO_3^- is removed from the extracellular fluid by renal excretion, which has the same effect as adding an H^+ to the extracellular fluid. This process helps return the H^+ concentration and pH toward normal.

Table 31-3 shows the overall extracellular fluid characteristics of respiratory and metabolic alkalosis. In *respiratory alkalosis*, there is an increase in extracellular fluid pH and a decrease in H^+ concentration. *The cause of the alkalosis is decreased plasma P_{CO_2}, caused by hyperventilation.* Reduction in P_{CO_2} then leads to decreased renal tubular H^+ secretion. Consequently, there is not enough H^+ in the renal tubular fluid to react with all the HCO_3^- that is filtered. Therefore, the HCO_3^- that cannot react with H^+ is not reabsorbed and is excreted in the urine. This results in a decreased plasma HCO_3^- concentration and correction of the alkalosis. *Therefore, the compensatory response to a primary reduction in P_{CO_2} in respiratory alkalosis is a reduction in plasma HCO_3^- concentration, caused by increased renal excretion of HCO_3^-.*

In *metabolic alkalosis*, there is also decreased plasma H^+ concentration and increased pH. *The cause of metabolic alkalosis, however, is a rise in the extracellular fluid HCO_3^- concentration.* This rise is partly compensated for by a reduction in the respiration rate, which increases P_{CO_2} and helps return the extracellular fluid pH toward normal. In addition, increased HCO_3^- concentration in the extracellular fluid increases the filtered load of HCO_3^-, which, in turn, causes excess HCO_3^- over H^+ secreted in the renal tubular fluid. The excess HCO_3^- in the tubular fluid fails to be reabsorbed because there is no H^+ with which it can react, and it is excreted in the urine. *In metabolic alkalosis, the primary compensations are decreased ventilation, which raises P_{CO_2}, and increases renal HCO_3^- excretion, which helps compensate for the initial rise in extracellular fluid HCO_3^- concentration.*

Clinical Causes of Acid–Base Disorders

Respiratory Acidosis Results From Decreased Ventilation and Increased P_{CO_2}

From the previous discussion, it is obvious that any factor that decreases the rate of pulmonary ventilation also increases the P_{CO_2} of extracellular fluid. This causes an increase in H_2CO_3 and H^+ concentrations, thus resulting in acidosis. Because the acidosis is caused by an abnormality in respiration, it is called *respiratory acidosis*.

Respiratory acidosis can occur from pathological conditions that damage the respiratory centers or that decrease the ability of the lungs to eliminate CO_2. For example, damage to the respiratory center in the medulla oblongata can lead to respiratory acidosis. Also, obstruction of the passageways of the respiratory tract, pneumonia, emphysema, or decreased pulmonary membrane surface area, as well as any factor that interferes with exchange of gases between the blood and alveolar air, can cause respiratory acidosis.

In respiratory acidosis, the compensatory responses available are as follows: (1) the buffers of the body fluids; and (2) the kidneys, which require several days to compensate for the disorder.

Respiratory Alkalosis Results From Increased Ventilation and Decreased P_{CO_2}

Respiratory alkalosis is caused by excessive ventilation by the lungs. Rarely does this occur because of physical pathological conditions. However, a psychoneurosis can occasionally increase breathing to the extent that a person becomes alkalotic.

A physiological type of respiratory alkalosis occurs when a person ascends to a high altitude. The low oxygen content of the air stimulates respiration, which causes loss of CO_2 and development of mild respiratory alkalosis. Again, the major means for compensation are the chemical buffers of the body fluids and ability of the kidneys to increase HCO_3^- excretion.

Metabolic Acidosis Results From Decreased Extracellular Fluid HCO_3^- Concentration

The term *metabolic acidosis* refers to all other types of acidosis besides those caused by excess CO_2 in the body fluids. Metabolic acidosis can result from several general causes: (1) failure of the kidneys to excrete metabolic acids normally formed in the body; (2) formation of excess quantities of metabolic acids in the body; (3) addition of metabolic acids to the body by ingestion or infusion of acids; and (4) loss of base from the body fluids, which has the same effect as adding an acid to the body fluids. Some specific conditions that cause metabolic acidosis are described in the following sections.

Renal Tubular Acidosis. Renal tubular acidosis results from a defect in renal secretion of H^+, reabsorption of HCO_3^-, or both. These disorders are generally of two types: (1) impairment of renal tubular HCO_3^- reabsorption, causing loss of HCO_3^- in the urine; or (2) inability of the renal tubular H^+ secretory mechanism to establish normal acidic urine, causing the excretion of alkaline urine. In these cases, inadequate amounts of titratable acid and NH_4^+ are excreted, so there is net accumulation of acid in the body fluids. Some causes of renal tubular acidosis include *chronic renal failure*, *insufficient aldosterone secretion* (Addison disease), and several hereditary and acquired disorders that impair tubular function, such as *Fanconi syndrome* (see Chapter 32).

Diarrhea. Severe diarrhea is probably the most frequent cause of metabolic acidosis. *The cause of this acidosis is the loss of large amounts of sodium bicarbonate into the feces.* The gastrointestinal secretions normally contain large amounts of bicarbonate, and diarrhea results in the loss of HCO_3^- from the body, which has the same effect as losing large amounts of bicarbonate in the urine. This form of metabolic acidosis can be serious and can cause death, especially in young children.

Vomiting of Intestinal Contents. Vomiting of gastric contents alone would cause a loss of acid and a tendency toward alkalosis because the stomach secretions are highly acidic. However, vomiting large amounts from deeper in the gastrointestinal tract causes loss of bicarbonate and results in metabolic acidosis in the same way that diarrhea causes acidosis.

Diabetes Mellitus. Diabetes mellitus is caused by lack of insulin secretion by the pancreas (type 1 diabetes) or by insufficient insulin secretion to compensate for decreased sensitivity to the effects of insulin (type 2 diabetes). In the absence of sufficient insulin, the normal metabolism of glucose is prevented. Instead, some of the fats are split into acetoacetic acid, and this acid is metabolized by the tissues for energy in place of glucose. With severe diabetes mellitus, blood acetoacetic acid levels can rise very high, causing severe metabolic acidosis. In an attempt to compensate for this acidosis, large amounts of acid are excreted in the urine—sometimes as much as 500 mmol/day.

Ingestion of Acids. Rarely are large amounts of acids ingested in normal foods. However, severe metabolic acidosis occasionally results from the ingestion of certain acidic poisons. Some of these substances include some acetylsalicylic compounds (e.g., aspirin) and methyl alcohol, which forms formic acid when it is metabolized.

Chronic Renal Failure. When kidney function declines markedly, there is a buildup in the body fluids of the anions of weak acids that are not being excreted by the kidneys. In addition, the decreased glomerular filtration rate reduces excretion of phosphates and NH_4^+, which reduces the amount of HCO_3^- added back to the body fluids. Thus, chronic renal failure can be associated with severe metabolic acidosis.

Metabolic Alkalosis Results From Increased Extracellular Fluid HCO_3^- Concentration

Excess retention of HCO_3^- or loss of H^+ from the body causes metabolic alkalosis. Metabolic alkalosis is not nearly as common as metabolic acidosis, but some of the causes of metabolic alkalosis are described in the following sections.

Administration of Diuretics (Except Carbonic Anhydrase Inhibitors). All diuretics cause increased flow of fluid along the tubules, usually increasing flow in the distal and collecting tubules. This effect leads to increased reabsorption of Na^+ from these parts of the nephrons. Because the sodium reabsorption here is coupled with H^+ secretion, the enhanced sodium reabsorption also leads to an increase in H^+ secretion and increase in bicarbonate reabsorption. Reductions in extracellular fluid volume associated with the use of diuretics is also generally associated with increased formation of Ang II and aldosterone, which both stimulate H^+ secretion and HCO_3^- reabsorption. These changes lead to the development of alkalosis, characterized by increased extracellular fluid bicarbonate concentration.

Excess Aldosterone. When large amounts of aldosterone are secreted by the adrenal glands, a mild metabolic alkalosis develops. As discussed previously, aldosterone promotes extensive reabsorption of Na^+ from the distal and collecting tubules and, at the same time, stimulates secretion of H^+ and HCO_3^- reabsorption by the intercalated cells of the collecting tubules. This increased secretion of H^+ and HCO_3^- reabsorption leads to metabolic alkalosis.

Vomiting of Gastric Contents. Vomiting of the gastric contents alone, without vomiting of the lower gastrointestinal contents, causes loss of the HCl secreted by the stomach mucosa. The net result is loss of acid from the extracellular fluid and development of metabolic alkalosis. This type of alkalosis occurs especially in neonates who have pyloric stenosis caused by hypertrophied pyloric sphincter muscles.

Ingestion of Alkaline Drugs. A common cause of metabolic alkalosis is ingestion of alkaline drugs, such as sodium bicarbonate, for the treatment of gastritis or peptic ulcer.

Treatment of Acidosis or Alkalosis

The best treatment for acidosis or alkalosis is to correct the condition that caused the abnormality. This is often difficult, especially in chronic diseases that cause impaired lung function or kidney failure. In these circumstances, various agents can be used to neutralize the excess acid or base in the extracellular fluid.

To neutralize excess acid, large amounts of *sodium bicarbonate* can be ingested by mouth. The sodium bicarbonate is absorbed from the gastrointestinal tract into the blood and increases the HCO_3^- portion of the bicarbonate buffer system, thereby increasing pH toward normal. Sodium bicarbonate can also be infused intravenously but, because of the potentially dangerous physiological effects of such treatment, other substances are often used instead, such as *sodium lactate* and *sodium gluconate*. The lactate and gluconate portions of the molecules are metabolized in the body, leaving the sodium in the extracellular fluid in the form of sodium bicarbonate and thereby increasing the pH of the fluid toward normal.

For the treatment of alkalosis, *ammonium chloride* can be administered by mouth. When ammonium chloride is absorbed into the blood, the ammonia portion is converted by the liver into urea. This reaction liberates HCl, which immediately reacts with the buffers of the body fluids to shift the H^+ concentration in the acidic direction. Ammonium chloride occasionally is infused intravenously, but NH_4^+ is highly toxic, and this procedure can be dangerous. The most appropriate treatment is to reverse the underlying cause of the alkalosis. For example, if metabolic alkalosis is associated with extracellular fluid volume depletion, but not heart failure, appropriate repletion of volume by infusion of isotonic saline solution is often beneficial in correcting the alkalosis.

Clinical Measurements and Analysis of Acid–Base Disorders

The appropriate therapy of acid–base disorders requires proper diagnosis. The simple acid–base disorders described previously can be diagnosed by analyzing three measurements from an arterial blood sample: pH, plasma HCO_3^- concentration, and P_{CO_2}.

The diagnosis of simple acid–base disorders involves several steps, as shown in **Figure 31-10**. By examining the pH, one can determine whether the disorder is acidosis or alkalosis. A pH less than 7.4 indicates acidosis, whereas a pH greater than 7.4 indicates alkalosis.

The second step is to examine the plasma P_{CO_2} and HCO_3^- concentrations. The normal value for P_{CO_2} is about 40 mm Hg, and for HCO_3^- it is 24 mEq/L. If the disorder has been characterized as acidosis and the plasma P_{CO_2} is increased, there must be a respiratory component to the acidosis. After renal compensation, the plasma HCO_3^- concentration in respiratory acidosis would tend to increase above normal. *Therefore, the expected values for a simple respiratory acidosis would be reduced plasma pH, increased P_{CO_2}, and increased plasma HCO_3^- concentration after partial renal compensation.*

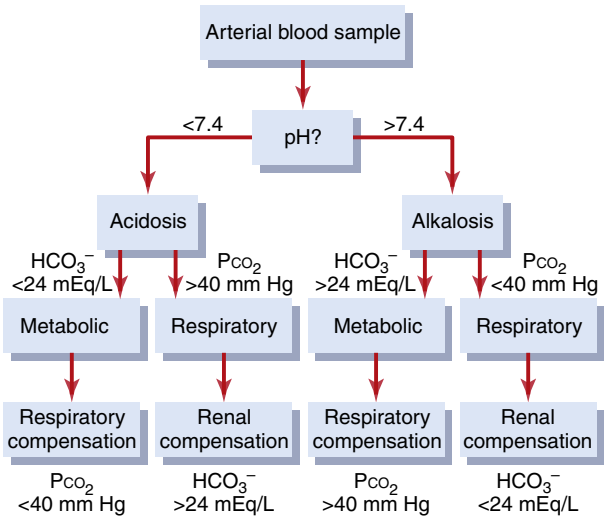


Figure 31-10. Analysis of simple acid–base disorders. If the compensatory responses are markedly different from those shown at the bottom of the figure, one should suspect a mixed acid–base disorder.

For metabolic acidosis, there would also be a decrease in plasma pH. However, with metabolic acidosis, the primary abnormality is a decrease in plasma HCO_3^- concentration. Therefore, if a low pH is associated with a low HCO_3^- concentration, there must be a metabolic component to the acidosis. In simple metabolic acidosis, the P_{CO_2} is reduced because of partial respiratory compensation, in contrast to respiratory acidosis, in which P_{CO_2} is increased. *Therefore, in simple metabolic acidosis, one would expect to find a low pH, a low plasma HCO_3^- concentration, and a reduction in P_{CO_2} after partial respiratory compensation.*

The procedures for categorizing the types of alkalosis involve the same basic steps. First, alkalosis implies that there is an increase in plasma pH. If the increase in pH is associated with decreased P_{CO_2}, there must be a respiratory component to the alkalosis. If the rise in pH is associated with increased HCO_3^-, there must be a metabolic component to the alkalosis. *Therefore, in simple respiratory alkalosis, one would expect to find increased pH, decreased P_{CO_2}, and decreased HCO_3^- concentration in the plasma. In simple metabolic alkalosis, one would expect to find increased pH, increased plasma HCO_3^-, and increased P_{CO_2}.*

Complex Acid–Base Disorders and Use of Acid–Base Nomogram for Diagnosis

In some cases, acid–base disorders are not accompanied by appropriate compensatory responses. When this situation occurs, the abnormality is referred to as a *mixed acid–base disorder*, which means that there are two or more underlying causes for the acid–base disturbance. For example, a patient with a low pH would be categorized as acidotic. If the disorder was metabolically mediated, this would also be accompanied by a low plasma HCO_3^- concentration and, after appropriate respiratory compensation, a low P_{CO_2}. However, if the low plasma pH and low HCO_3^- concentration are associated with an elevated P_{CO_2}, one would suspect a respiratory component to the acidosis, as well as a metabolic component. Therefore, this disorder would be categorized as a mixed acidosis. This disorder could occur, for example, in a patient with acute

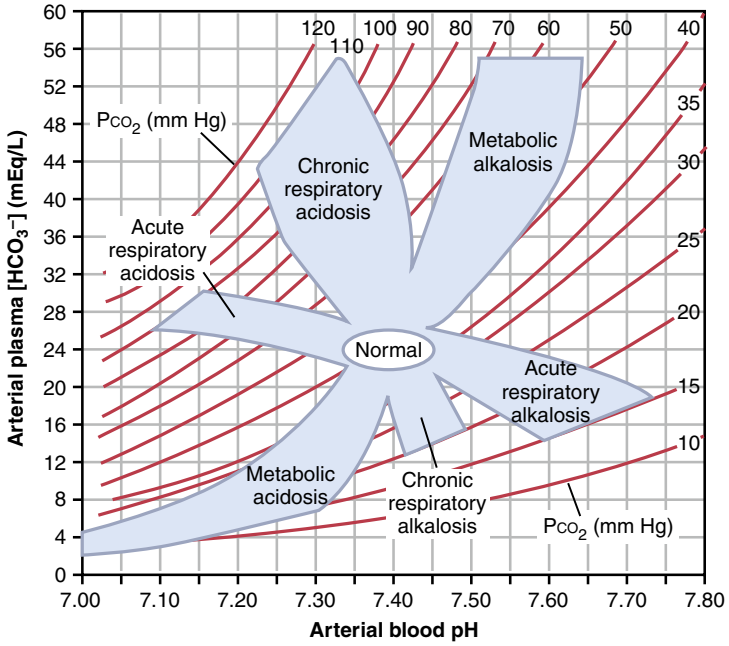


Figure 31-11. Acid–base nomogram showing arterial blood pH, arterial plasma HCO_3^-, and P_{CO_2} values. The *central open circle* shows the approximate limits for acid–base status in normal people. The *shaded areas* in the nomogram show the approximate limits for the normal compensations caused by simple metabolic and respiratory disorders. For values lying outside the shaded areas, one should suspect a mixed acid–base disorder. (*Modified from Cogan MG, Rector FC Jr: Acid-Base Disorders in the Kidney, 3rd ed. Philadelphia: WB Saunders, 1986.*)

HCO_3^- loss from the gastrointestinal tract because of diarrhea (metabolic acidosis) and emphysema (respiratory acidosis).

A convenient way to diagnose acid–base disorders is to use an acid–base nomogram, as shown in **Figure 31-11**. This diagram can be used to determine the type of acidosis or alkalosis, as well as its severity. In this acid–base diagram, pH, HCO_3^- concentration, and P_{CO_2} values intersect according to the Henderson-Hasselbalch equation. The central open circle shows normal values and the deviations that can still be considered within the normal range. The shaded areas of the diagram show the 95% confidence limits for the normal compensations to simple metabolic and respiratory disorders.

When using this diagram, one must assume that sufficient time has elapsed for a full compensatory response, which is 6 to 12 hours for the ventilatory compensations in primary metabolic disorders and 3 to 5 days for the metabolic compensations in primary respiratory disorders. If a value is within the shaded area, this suggests that there is a simple acid–base disturbance. Conversely, if the values for pH, bicarbonate, or P_{CO_2} lie outside the shaded area, this suggests that the patient may have a mixed acid–base disorder.

It is important to recognize that an acid–base value within the shaded area does not *always* mean that a simple acid–base disorder is present. With this reservation in mind, the acid–base diagrams can be used as a quick means of determining the specific type and severity of an acid–base disorder.

For example, assume that the arterial plasma from a patient yields the following values: pH, 7.30; plasma HCO_3^- concentration, 12.0 mEq/L; and plasma P_{CO_2}, 25 mm Hg. With these values, one can look at the diagram and find that this represents a simple metabolic acidosis, with appropriate respiratory compensation that reduces the P_{CO_2} from its normal value of 40 mm Hg to 25 mm Hg.

A second example would be a patient with the following values: pH, 7.15; plasma HCO_3^- concentration, 17 mEq/L; and plasma P_{CO_2}, 50 mm Hg. In this example, the patient is acidotic, and there appears to be a metabolic component because the plasma HCO_3^- concentration is lower than the normal value of 24 mEq/L. However, the respiratory compensation that would normally reduce P_{CO_2} is absent and P_{CO_2} is slightly increased above the normal value of 40 mm Hg. This finding is consistent with a mixed acid–base disturbance consisting of metabolic acidosis, as well as a respiratory component.

The acid–base nomogram serves as a quick way to assess the type and severity of disorders that may be contributing to abnormal pH, P_{CO_2}, and plasma bicarbonate concentrations. In a clinical setting, the patient's history and other physical findings also provide important clues concerning the causes and treatment of the acid–base disorders.

Use of Anion Gap to Diagnose Acid–Base Disorders

The concentrations of anions and cations in plasma must be equal to maintain electrical neutrality. Therefore, there is no real anion gap in the plasma. However, only certain cations and anions are routinely measured in the clinical laboratory. The cation normally measured is Na^+, and the anions are usually Cl^- and HCO_3^-. The anion gap—which is only a diagnostic concept— is the difference between unmeasured anions and unmeasured cations and is estimated as follows:

$$\text{Plasma anion gap} = [Na^+] - [HCO_3^-] - [Cl^-]$$
$$= 144 - 24 - 108 = 12 \text{ mEq/L}$$

The anion gap will increase if unmeasured anions rise or if unmeasured cations fall. The most important unmeasured cations include calcium, magnesium, and potassium, and the major unmeasured anions are albumin, phosphate, sulfate, and other organic anions. Usually, the unmeasured anions exceed the unmeasured cations, and the anion gap ranges between 8 and 16 mEq/L.

Table 31-4 Metabolic Acidosis Associated With Normal or Increased Plasma Anion Gap

Increased Anion Gap (Normochloremia)	Normal Anion Gap (Hyperchloremia)
Diabetes mellitus (ketoacidosis)	Diarrhea
Lactic acidosis	Renal tubular acidosis
Chronic renal failure	Carbonic anhydrase inhibitors
Aspirin (acetylsalicylic acid) poisoning	Addison disease
Methanol poisoning	
Ethylene glycol poisoning	
Starvation	

The plasma anion gap is used mainly in diagnosing different causes of metabolic acidosis. In metabolic acidosis, plasma HCO_3^- concentration is reduced. If plasma sodium concentration is unchanged, the concentration of anions (Cl^- or an unmeasured anion) increases to maintain electroneutrality. If plasma Cl^- increases in proportion to the fall in plasma HCO_3^-, the anion gap will remain normal. This is often referred to as *hyperchloremic metabolic acidosis*.

If the decrease in plasma HCO_3^- is not accompanied by increased Cl^-, there must be increased levels of unmeasured anions and therefore an increase in the calculated anion gap. Metabolic acidosis caused by excess nonvolatile acids (besides HCl), such as lactic acid or ketoacids, is associated with an increased plasma anion gap because the fall in HCO_3^- is not matched by an equal increase in Cl^-. Some examples of metabolic acidosis associated with a normal or increased anion gap are shown in **Table 31-4**. By calculating the anion gap, one can narrow some of the potential causes of metabolic acidosis.

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