Chapter 27: Fluid, Electrolyte, and Acid–Base Balance

Fluid, Electrolyte, and Acid–Base Balance: An Overview, p. 995

- Most of your body weight is water. Water accounts for up to 99 percent of the volume of the fluid outside cells, and it is an essential ingredient of cytoplasm. All of a cell’s operations rely on water as a diffusion medium for the distribution of gases, nutrients, and waste products.
- To survive, we must maintain a normal volume and composition of both the extracellular fluid or ECF (the interstitial fluid, plasma, and other body fluids), and the intracellular fluid or ICF (the cytosol). The ionic concentrations and pH (hydrogen ion concentration) of these fluids are as important as their absolute quantities.
- Stabilizing the volumes, solute concentrations, and pH of the ECF and the ICF involves three interrelated processes:
  - Fluid Balance. You are in fluid balance when the amount of water you gain each day is equal to the amount you lose to the environment. The maintenance of normal fluid balance involves regulating the content and distribution of body water in the ECF and the ICF. The digestive system is the primary source of water gains; a small amount of additional water is generated by metabolic activity. The urinary system is the primary route for water loss under normal conditions. Although cells and tissues cannot transport water, they can transport ions and create concentration gradients that are then eliminated by osmosis.
  - Electrolyte Balance. Electrolytes are ions released through the dissociation of inorganic compounds; they are so named because they can conduct an electrical current in a solution. If the gains and losses for every electrolyte are in balance, you are said to be in electrolyte balance. Electrolyte balance primarily involves balancing the rates of absorption across the digestive tract with rates of loss at the kidneys, although losses at sweat glands and other sites can play a secondary role.
  - Acid–Base Balance. You are in acid–base balance when the production of hydrogen ions in your body is precisely offset by their loss. When acid–base balance exists, the pH of body fluids remains within normal limits. Preventing a reduction in pH is the primary problem, because your body generates a variety of acids during normal metabolic operations. The kidneys play a major role by secreting hydrogen ions into the urine and generating buffers that enter the bloodstream. Such secretion occurs primarily in the distal segments of the distal convoluted tubule (DCT) and along the collecting system. The lungs also play a key role through the elimination of carbon dioxide.

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- Water accounts for roughly 60 percent of the total body weight of an adult male, and 50 percent of that of an adult female. This difference between the sexes primarily reflects the proportionately larger mass of adipose tissue in adult females, and the greater average muscle mass in adult males. In both sexes, intracellular fluid contains a greater proportion of total body water than does extracellular fluid.
- Exchange between the ICF and the ECF occurs across cell membranes by osmosis, diffusion, and carrier-mediated transport.

The ECF and the ICF

- The largest subdivisions of the ECF are the interstitial fluid of peripheral tissues and the plasma of circulating blood. Minor components of the ECF include lymph, cerebrospinal fluid (CSF), synovial fluid, serous fluids (pleural, pericardial, and peritoneal fluids), aqueous humor, perilymph, and endolymph.
- The greatest variation is in the ICF, as a result of differences in the intracellular water content of fat versus muscle. Less striking differences occur in the ECF values, due to variations in the interstitial fluid volume of various tissues and the larger blood volume in males versus females.
Exchange among the subdivisions of the ECF occurs primarily across the endothelial lining of capillaries. Fluid may also travel from the interstitial spaces to plasma through lymphatic vessels that drain into the venous system.

- The ECF and ICF are called fluid compartments, because they commonly behave as distinct entities. The presence of a cell membrane and active transport at the membrane surface enable cells to maintain internal environments with a composition that differs from their surroundings.

- The principal ions in the ECF are sodium, chloride, and bicarbonate. The ICF contains an abundance of potassium, magnesium, and phosphate ions, plus large numbers of negatively charged proteins.

- If the cell membrane were freely permeable, diffusion would continue until these ions were evenly distributed across the membrane. But it does not, because cell membranes are selectively permeable: ions can enter or leave the cell only via specific membrane channels. In addition, carrier mechanisms move specific ions into or out of the cell.

- Despite the differences in the concentration of specific substances, the osmotic concentrations of the ICF and ECF are identical. Osmosis eliminates minor differences in concentration almost at once, because most cell membranes are freely permeable to water.

- Because changes in solute concentrations lead to immediate changes in water distribution, the regulation of fluid balance and that of electrolyte balance are tightly intertwined.

**Basic Concepts in the Regulation of Fluids and Electrolytes**

- Before we can proceed to a discussion of fluid balance and electrolyte balance, you must understand four basic principles:
  - All the Homeostatic Mechanisms That Monitor and Adjust the Composition of Body
  - No Receptors Directly Monitor Fluid or Electrolyte Balance. In other words, receptors cannot detect how many liters of water or grams of sodium, chloride, or potassium the body contains, or count how many liters or grams we gain or lose in the course of a day. But receptors can monitor plasma volume and osmotic concentration.
  - Cells Cannot Move Water Molecules by Active Transport. All movement of water across cell membranes and epithelia occurs passively, in response to osmotic gradients established by the active transport of specific ions, such as sodium and chloride.
  - The Body’s Content of Water or Electrolytes Will Rise if Dietary Gains Exceed Losses to the Environment, and Will Fall if Losses Exceed Gains.

**An Overview of the Primary Regulatory Hormones**

- Major physiological adjustments affecting fluid balance and electrolyte balance are mediated by three hormones:
  - **Antidiuretic Hormone** The hypothalamus contains special cells known as osmoreceptors, which monitor the osmotic concentration of the ECF. These cells are sensitive to subtle changes: A 2 percent change in osmotic concentration (approximately ) is sufficient to alter osmoreceptor activity. The population of osmoreceptors includes neurons that secrete ADH. These neurons are located in the anterior hypothalamus, and their axons release ADH near fenestrated capillaries in the posterior lobe of the pituitary gland. The rate of ADH release varies directly with osmotic concentration: The higher the osmotic concentration, the more ADH is released. Increased release of ADH has two important effects:
    - It stimulates water conservation at the kidneys, reducing urinary water losses and concentrating the urine
    - it stimulates the thirst center, promoting the intake of fluids.
  - **Aldosterone** The secretion of aldosterone by the adrenal cortex plays a major role in determining the rate of absorption and loss along the distal convoluted tubule (DCT) and collecting system of the kidneys. The higher the plasma concentration of aldosterone, the more efficiently the kidneys conserve Because “water follows salt,” the conservation of Na⁺ also stimulates water retention. Aldosterone also increases the sensitivity of salt receptors on the tongue. This effect may increase your interest in, and consumption of, salty foods. Aldosterone is secreted in response to
rising or falling levels in the blood reaching the adrenal cortex, or in response to the activation of the renin–angiotensin system.

- **Natriuretic Peptides** The natriuretic peptides ANP and BNP are released by cardiac muscle cells in response to abnormal stretching of the heart walls, caused by elevated blood pressure or an increase in blood volume. Among their other effects, they reduce thirst and block the release of ADH and aldosterone that might otherwise lead to the conservation of water and salt. The resulting diuresis (fluid loss at the kidneys) lowers both blood pressure and plasma volume, eliminating the source of the stimulation.

### The Interplay between Fluid Balance and Electrolyte Balance

- At first glance, it can be very difficult to distinguish between water balance and electrolyte balance. For example, when you lose body water, plasma volume decreases and electrolyte concentrations rise. Conversely, when you gain or lose excess electrolytes, there is an associated water gain or loss due to osmosis.

### Fluid Balance, p. 999

- Water circulates freely within the ECF compartment. At capillary beds throughout the body, hydrostatic pressure forces water out of plasma and into interstitial spaces. Some of that water is reabsorbed along the distal portion of the capillary bed, and the rest enters lymphatic vessels for transport to the venous circulation. There is also a continuous movement of fluid among the minor components of the ECF:

#### Fluid Movement within the ECF

- The exchange between plasma and interstitial fluid, by far the largest components of the ECF, is determined by the relationship between the net hydrostatic pressure, which tends to push water out of the plasma and into the interstitial fluid, and the net colloid osmotic pressure, which tends to draw water out of the interstitial fluid and into the plasma. The interaction between these opposing forces results in the continuous filtration of fluid from the capillaries into the interstitial fluid.
- This volume of fluid is then redistributed: After passing through the channels of the lymphatic system, the fluid returns to the venous system. At any moment, interstitial fluid and minor fluid compartments contain roughly 80 percent of the ECF volume, and plasma contains the other 20 percent.
- Any factor that affects the net hydrostatic pressure or the net colloid osmotic pressure will alter the distribution of fluid within the ECF. The movement of abnormal amounts of water from plasma into interstitial fluid is called *edema*.

### Fluid Gains and Losses

- **Water Losses**. You lose roughly 2500 ml of water each day through urine, feces, and *insensible perspiration*—the gradual movement of water across the epithelia of the skin and respiratory tract. The losses due to *sensible perspiration*—the secretory activities of the sweat glands—vary with the activities you undertake. Sensible perspiration can cause significant water deficits, with maximum perspiration rates reaching 4 liters per hour. Fever can also increase water losses.
- **Water Gains**. A water gain of roughly 2500 ml day is required to balance your average water losses. This value amounts to roughly 0.5 percent of body weight per day. You obtain water through eating (1000 ml), drinking (1200 ml), and *metabolic generation* (300 ml). Metabolic generation of water is the production of water within cells, primarily as a result of oxidative phosphorylation in mitochondria.

### Fluid Shifts

- A rapid water movement between the ECF and the ICF in response to an osmotic gradient is called a fluid shift. Fluid shifts occur rapidly in response to changes in the osmotic concentration of the ECF and reach equilibrium within minutes to hours.
  - If the Osmotic Concentration of the ECF Increases, that Fluid Will Become Hypertonic with Respect to the ICF. Water will then move from the cells into the ECF until osmotic equilibrium is restored. The osmotic concentration of the ECF will increase if you lose water but retain electrolytes.
  - If the Osmotic Concentration of the ECF Decreases, that Fluid Will Become Hypotonic with Respect to the ICF. Water will then move from the ECF into the cells, and the ICF volume will increase. The osmotic concentration of the ECF will decrease if you gain water but do not gain...
electrolytes. Because the volume of the ICF is much greater than that of the ECF, the ICF acts as a water reserve. In effect, instead of a large change in the osmotic concentration of the ECF, smaller changes occur in both the ECF and ICF.

- **Allocation of Water Losses** Dehydration, or water depletion, develops when water losses outpace water gains. When you lose water but retain electrolytes, the osmotic concentration of the ECF rises. Osmosis then moves water out of the ICF and into the ECF until the two solutions are again isotonic. At that point, both the ECF and ICF are somewhat more concentrated than normal, and both volumes are lower than they were before the fluid loss.
  - Conditions that cause severe water losses include excessive perspiration (brought about by exercising in hot weather), inadequate water consumption, repeated vomiting, and diarrhea. Homeostatic responses include physiologic mechanisms (ADH and renin secretion) and behavioral changes (increasing fluid intake, preferably as soon as possible).

- **Distribution of Water Gains** When you drink a glass of pure water or when you are given hypotonic solutions intravenously, your body’s water content increases without a corresponding increase in the concentration of electrolytes. As a result, the ECF increases in volume but becomes hypotonic with respect to the ICF. A fluid shift then occurs, and the volume of the ICF increases at the expense of the ECF. Once again, the larger volume of the ICF limits the amount of osmotic change. After the fluid shift, the ECF and ICF have slightly larger volumes and slightly lower osmotic concentrations than they did originally. Normally, this situation will be promptly corrected.
  - If the situation is not corrected, a variety of clinical problems will develop as water shifts into the intracellular fluid, distorting cells, changing the solute concentrations around enzymes, and disrupting normal cell functions. This condition is called overhydration, or water excess. It can be caused by (1) the ingestion of a large volume of fresh water or the infusion (injection into the bloodstream) of a hypotonic solution; (2) an inability to eliminate excess water in urine, due to chronic renal failure, heart failure, cirrhosis, or some other disorder; and (3) endocrine disorders, such as excessive ADH production.
  - The most obvious sign of overhydration is abnormally low sodium ion concentrations (hyponatremia), and the reduction in concentrations in the ECF leads to a fluid shift into the ICF. The first signs are the effects on central nervous system function. The individual initially behaves as if drunk on alcohol. This condition, called water intoxication is extremely dangerous. Untreated cases can rapidly progress from confusion to hallucinations, convulsions, coma, and then death.

**Electrolyte Balance, p. 1002**

- You are in electrolyte balance when the rates of gain and loss are equal for each electrolyte in your body. Electrolyte balance is important because:
  - Total electrolyte concentrations directly affect water balance, as previously described
  - The concentrations of individual electrolytes can affect cell functions.
- Sodium is the dominant cation in the ECF. More than 90 percent of the osmotic concentration of the ECF results from the presence of sodium salts, mainly sodium chloride (NaCl) and sodium bicarbonate so changes in the osmotic concentration of body fluids generally reflect changes in concentration. Normal concentrations in the ECF average about 140meq/L versus 10meq/L or less in the ICF.
- Potassium is the dominant cation in the ICF, where concentrations reach 160 meq/L. Extracellular concentrations are generally very low, from 3.8 to 5.0 meq/L.
- Two general rules concerning sodium balance and potassium balance are worth noting:
  - The Most Common Problems with Electrolyte Balance Are Caused by an Imbalance between Gains and Losses of Sodium Ions.
  - Problems with Potassium Balance Are Less Common, but Significantly More Dangerous than Are Those Related to Sodium Balance.
**Sodium Balance**

- The total amount of sodium in the ECF represents a balance between two factors:
  - **Sodium Ion Uptake across the Digestive Epithelium.** Sodium ions enter the ECF by crossing the digestive epithelium through diffusion and carrier-mediated transport. The rate of absorption varies directly with the amount of sodium in the diet.
  - **Sodium Ion Excretion at the Kidneys and Other Sites.** Sodium losses occur primarily by excretion in urine and through perspiration. The kidneys are the most important sites of regulation.
- A person in sodium balance typically gains and loses 48–144 mEq (1.1–3.3 g) of Na⁺ each day. When sodium gains exceed sodium losses, the total content of the ECF goes up; when losses exceed gains, the content declines. However, a change in the content of the ECF does not produce a change in the concentration. When sodium intake or output changes, a corresponding gain or loss of water tends to keep the concentration constant.
- When sodium losses exceed gains, the volume of the ECF decreases. This reduction occurs without a significant change in the osmotic concentration of the ECF. Thus, if you perspire heavily but consume only pure water, you will lose sodium, and the osmotic concentration of the ECF will drop briefly. However, as soon as the osmotic concentration drops by 2 percent or more, ADH secretion decreases, so water losses at your kidneys increase. As water leaves the ECF, the osmotic concentration returns to normal. Minor changes in ECF volume do not matter, because they do not cause adverse physiological effects.
- If regulation of concentrations results in a large change in ECF volume, the situation will be corrected by the same homeostatic mechanisms responsible for regulating blood volume and blood pressure. This is the case because when ECF volume changes, so does plasma volume and, in turn, blood volume. If ECF volume rises, blood volume goes up; if ECF volume drops, blood volume goes down.
- A rise in blood volume elevates blood pressure; a drop lowers blood pressure. The net result is that homeostatic mechanisms can monitor ECF volume indirectly by monitoring blood pressure. The receptors involved are baroreceptors at the carotid sinus, the aortic sinus, and the right atrium.
- Sustained abnormalities in the concentration in the ECF occur only when there are severe problems with fluid balance, such as dehydration or overhydration. When the body’s water content rises enough to reduce the concentration of the ECF below a state of hyponatremia exists. When the body water content declines, the concentration rises; when that concentration exceeds hypernatremia exists.
- If the ECF volume is inadequate, both blood volume and blood pressure decline, and the renin–angiotensin system is activated. In response, losses of water and are reduced, and gains of water and are increased. The net result is that ECF volume increases. Although the total amount of in the ECF is increasing (gains exceed losses), the concentration in the ECF remains unchanged, because absorption is accompanied by osmotic water movement.
- If the plasma volume becomes abnormally large, venous return increases, stretching the atrial and ventricular walls and stimulating the release of natriuretic peptides (ANP and BNP). This in turn reduces thirst and blocks the secretion of ADH and aldosterone, which together promote water or salt conservation. As a result, salt and water loss at the kidneys increases and the volume of the ECF declines.

**Potassium Balance**

- Roughly 98 percent of the potassium content of the human body is in the ICF. Cells expend energy to recover potassium ions as they diffuse out of the cytoplasm and into the ECF. The concentration outside the cell is relatively low, and the concentration in the ECF at any moment represents a balance between (1) the rate of gain across the digestive epithelium and (2) the rate of loss into urine.
- Potassium loss in urine is regulated by controlling the activities of ion pumps along the distal portions of the nephron and collecting system. Whenever a sodium ion is reabsorbed from the tubular fluid, it generally is exchanged for a cation (typically K⁺) in the peritubular fluid.
Urinary losses are usually limited to the amount gained by absorption across the digestive epithelium, typically 50–150 mEq (1.9–5.8 g) per day. The concentration in the ECF is controlled by adjustments in the rate of active secretion along the distal convoluted tubule and collecting system of the nephron. The rate of tubular secretion of varies in response to three factors:

- **Changes in the Concentration of the ECF.** In general, the higher the extracellular concentration of potassium, the higher the rate of secretion.
- **Changes in pH.** When the pH of the ECF falls, so does the pH of peritubular fluid. The rate of potassium secretion then declines, because hydrogen ions, rather than potassium ions, are secreted in exchange for sodium ions in tubular fluid.
- **Aldosterone Levels.** The rate at which K\(^+\) is lost in urine is strongly affected by aldosterone, because the ion pumps that are sensitive to this hormone reabsorb from filtrate in exchange for from peritubular fluid. Aldosterone secretion is stimulated by angiotensin II as part of the regulation of blood volume. High plasma concentrations also stimulate aldosterone secretion directly.

**Balance of Other Electrolytes**

- **Calcium Balance** Calcium is the most abundant mineral in the body. A typical individual has 1–2 kg (2.2–4.4 lb) of this element, 99 percent of which is deposited in the skeleton. In addition to forming the crystalline component of bone, calcium ions play key roles in the control of muscular and neural activities, in blood clotting, as cofactors for enzymatic reactions, and as second messengers.
  - The hormones parathyroid hormone (PTH), calcitriol, and (to a lesser degree) calcitonin maintain calcium homeostasis in the ECF. Parathyroid hormone and calcitriol raise concentrations; their actions are opposed by calcitonin.
  - A small amount of Ca\(^{2+}\) is lost in the bile, and under normal circumstances very little escapes in urine or feces. To keep pace with biliary, urinary, and fecal losses, an adult must absorb only 0.8-1.2 g/day of Ca\(^{2+}\). That amount represents only about 0.03 percent of the calcium reserve in the skeleton.
  - Calcium absorption at the digestive tract and reabsorption along the distal convoluted tubule are stimulated by PTH from the parathyroid glands and calcitriol from the kidneys.
  - **Hypercalcemia** exists when the concentration of the ECF exceeds The primary cause of hypercalcemia in adults is hyperparathyroidism, a condition resulting from oversecretion of PTH. Less common causes include malignant cancers of the breast, lung, kidney, and bone marrow, and excessive use of calcium or vitamin D supplements.
  - **Hypocalcemia** (a concentration under ) is much less common than hypercalcemia. Hypoparathyroidism (undersecretion of PTH), vitamin D deficiency, or chronic renal failure is typically responsible for hypocalcemia.

- **Magnesium Balance** The adult body contains about 29 g of magnesium; almost 60 percent of it is deposited in the skeleton. The magnesium in body fluids is contained primarily in the ICF, where the concentration of Mg\(^{2+}\) averages about 26 mg/L. Magnesium is required as a cofactor for several important enzymatic reactions, including the phosphorylation of glucose within cells and the use of ATP by contracting muscle fibers. Magnesium is also important as a structural component of bone.
  - The Mg\(^{2+}\) concentration of the ECF averages about considerably lower than levels in the ICF. The proximal convoluted tubule reabsorbs magnesium very effectively. Keeping pace with the daily urinary loss requires a minimum dietary intake of only 24–32 mEq (0.3–0.4 g) per day.

- **Phosphate Balance** Phosphate ions are required for bone mineralization, and roughly 740 g of PO\(_4\)\(^{3-}\) is bound up in the mineral salts of the skeleton. In body fluids, the most important functions of PO\(_4\)\(^{3-}\) involve the ICF, where the ions are required for the formation of high-energy compounds, the activation of enzymes, and the synthesis of nucleic acids. The PO\(_4\)\(^{3-}\) concentration of the plasma is usually 1.8–2.6 mEq L. Phosphate ions are reabsorbed from tubular fluid along the proximal convoluted tubule; urinary and fecal losses of amount to 30–45 mEq (0.8–1.2 g) per day. Phosphate ion reabsorption along the PCT is stimulated by calcitriol.
**Chloride Balance** Chloride ions are the most abundant anions in the ECF. The plasma concentration ranges from 100-108 meq/L. In the ICF, Cl\(^{-}\) concentrations are usually low. Chloride ions are absorbed across the digestive tract together with sodium ions; several carrier proteins along the renal tubules reabsorb with Cl\(^{-}\) with Na\(^{+}\). The rate of loss is small; a gain of 48–146 mEq (1.7–5.1 g) per day will keep pace with losses in urine and perspiration.

**Acid–Base Balance, p. 1007**

- The pH of body fluids can be altered by the introduction of either acids or bases. In general, acids and bases can be categorized as either strong or weak.
  - **Strong acids** and **strong bases** dissociate completely in solution.
  - **When weak acids** or **weak bases** enter a solution, a significant number of molecules remain intact; dissociation is not complete. Thus, if you place molecules of a weak acid in one solution and the same number of molecules of a strong acid in another solution, the weak acid will liberate fewer hydrogen ions and have less effect on the pH of the solution than will the strong acid.

- Carbonic acid is a weak acid. At the normal pH of the ECF, an equilibrium state exists, and the reaction can be diagrammed as follows: \(\text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^-\).

**The Importance of pH Control**

- The pH of body fluids reflects interactions among all the acids, bases, and salts in solution in the body. The pH of the ECF normally remains within relatively narrow limits, usually 7.35–7.45. Any deviation from the normal range is extremely dangerous, because changes in concentrations disrupt the stability of cell membranes, alter the structure of proteins, and change the activities of important enzymes.
- When the pH of plasma falls below 7.35, **acidemia** exists. The physiological state that results is called **acidosis**. When the pH of plasma rises above 7.45, **alkalemia** exists. The physiological state that results is called **alkalosis**.
  - Acidosis and alkalosis affect virtually all body systems, but the nervous and cardiovascular systems are particularly sensitive to pH fluctuations.
  - The control of pH is therefore a homeostatic process of great physiological and clinical significance. Although both acidosis and alkalosis are dangerous, in practice problems with acidosis are much more common. This is so because several acids, including carbonic acid, are generated by normal cellular activities.

**Types of Acids in the Body**

- The body contains three categories of acids: (1) volatile acids, (2) fixed acids, and (3) organic acids.
- A volatile acid is an acid that can leave solution and enter the atmosphere. Carbonic acid is an important volatile acid in body fluids.
  - At the lungs, carbonic acid breaks down into carbon dioxide and water; the carbon dioxide diffuses into the alveoli. In peripheral tissues, carbon dioxide in solution interacts with water to form carbonic acid, which dissociates to release hydrogen ions and bicarbonate ions. This reaction occurs spontaneously in body fluids, but it proceeds much more rapidly in the presence of carbonic anhydrase (CA), an enzyme found in the cytoplasm of red blood cells, liver and kidney cells, parietal cells of the stomach, and many other types of cells.
  - Because most of the carbon dioxide in solution is converted to carbonic acid, and most of the carbonic acid dissociates, the partial pressure of carbon dioxide and the pH are inversely related. When carbon dioxide levels rise, additional hydrogen ions and bicarbonate ions are released, so the pH goes down.
- Fixed acids are acids that do not leave solution; once produced, they remain in body fluids until they are eliminated at the kidneys. Sulfuric acid and phosphoric acid are the most important fixed acids in the body. They are generated in small amounts during the catabolism of amino acids and compounds that contain phosphate groups, including phospholipids and nucleic acids.
Organic acids are acid participants in or by-products of aerobic metabolism. Important organic acids include lactic acid, produced by the anaerobic metabolism of pyruvate, and ketone bodies, synthesized from acetyl-CoA. Under normal conditions, most organic acids are metabolized rapidly, so significant accumulations do not occur. But relatively large amounts of organic acids are produced (1) during periods of anaerobic metabolism, because lactic acid builds up rapidly, and (2) during starvation or excessive lipid catabolism, because ketone bodies accumulate.

Mechanisms of pH Control

- To maintain acid–base balance over long periods of time, your body must balance gains and losses of hydrogen ions. Hydrogen ions are gained at the digestive tract and through metabolic activities within cells. Your body must eliminate these ions at the kidneys, by secreting into urine, and at the lungs, by forming water and carbon dioxide from and the sites of elimination are far removed from the sites of acid production.
- As the hydrogen ions travel through the body, they must be neutralized to avoid tissue damage. The acids produced in the course of normal metabolic operations are temporarily neutralized by buffers and buffer systems in body fluids. Buffers are dissolved compounds that stabilize the pH of a solution by providing or removing hydrogen ions that can donate and weak bases that can absorb hydroxide ions. A buffer system in body fluids generally consists of a combination of a weak acid and the anion released by its dissociation. The anion functions as a weak base.
- In solution, molecules of the weak acid exist in equilibrium with its dissociation products. The body has three major buffer systems, each with slightly different characteristics and distributions:
  - **Protein buffer systems** contribute to the regulation of pH in the ECF and ICF. These buffer systems interact extensively with the other two buffer systems.
  - **The carbonic acid–bicarbonate buffer system** is most important in the ECF.
  - **The phosphate buffer system** has an important role in buffering the pH of the ICF and of urine.
- **Protein Buffer Systems** Protein buffer systems depend on the ability of amino acids to respond to pH changes by accepting or releasing hydrogen ions. If pH climbs, the carboxyl group of the amino acid can dissociate, acting as a weak acid and releasing a hydrogen ion. The carboxyl group then becomes a carboxylate ion. At the normal pH of body fluids (7.35–7.45), the carboxyl groups of most amino acids have already given up their hydrogen ions.
- If pH drops, the carboxylate ion and the amino group can act as weak bases and accept additional hydrogen ions, forming a carboxyl group and an amino ion, respectively. This effect is limited primarily to free amino acids and to the last amino acid in a polypeptide chain, because the carboxyl and amino groups in peptide bonds cannot function as buffers.
- Plasma proteins contribute to the buffering capabilities of blood. Interstitial fluid contains extracellular protein fibers and dissolved amino acids that also assist in regulating pH. In the ICF of active cells, structural and other proteins provide an extensive buffering capability that prevents destructive changes in pH when organic acids, such as lactic acid or pyruvic acid, are produced by cellular metabolism.
- **The Hemoglobin Buffer System** The situation is somewhat different for red blood cells. These cells, which contain roughly 5.5 percent of the ICF, are normally suspended in the plasma. They are densely packed with hemoglobin, and their cytoplasm contains large amounts of carbonic anhydrase. Red blood cells have a significant effect on the pH of the ECF, because they absorb carbon dioxide from the plasma and convert it to carbonic acid.
  - Carbon dioxide can diffuse across the RBC membrane very quickly, so no transport mechanism is needed. As the carbonic acid dissociates, the bicarbonate ions diffuse into the plasma in exchange for chloride ions, a swap known as the chloride shift. The hydrogen ions are buffered by hemoglobin molecules.
  - At the lungs, the entire reaction sequence proceeds in reverse. This mechanism is known as the hemoglobin buffer system. The hemoglobin buffer system is the only intracellular buffer system
that can have an immediate effect on the pH of the ECF. The hemoglobin buffer system helps prevent drastic changes in pH when the plasma is rising or falling.

- The Carbonic Acid–Bicarbonate Buffer System With the exception of red blood cells, some cancer cells, and tissues temporarily deprived of oxygen, body cells generate carbon dioxide virtually 24 hours a day.
  - Most of the carbon dioxide is converted to carbonic acid, which then dissociates into a hydrogen ion and a bicarbonate ion. The carbonic acid and its dissociation products form the carbonic acid–bicarbonate buffer system. The primary role of the carbonic acid–bicarbonate buffer system is to prevent changes in pH caused by organic acids and fixed acids in the ECF.
  - Because the reaction is freely reversible, a change in the concentration of any participant affects the concentrations of all other participants.
  - The carbonic acid–bicarbonate buffer system can also protect against increases in pH, although such changes are relatively rare. If hydrogen ions are removed from the plasma, the reaction is driven to the right: The declines, and the dissociation of replaces the missing The carbonic acid–bicarbonate buffer system has three important limitations:
    - It Cannot Protect the ECF from Changes in pH that Result from Elevated or Depressed Levels of CO₂.
    - It Can Function Only When the Respiratory System and the Respiratory Control Centers Are Working Normally.
    - The Ability to Buffer Acids Is Limited by the Availability of Bicarbonate Ions
  - Problems due to a lack of bicarbonate ions are rare, for several reasons. First, body fluids contain a large reserve of primarily in the form of dissolved molecules of the weak base sodium bicarbonate. This readily available supply of HCO₃⁻ is known as the bicarbonate reserve.
- The Phosphate Buffer System The phosphate buffer system consists of the anion H₂PO₄⁻ which is a weak acid. The operation of the phosphate buffer system resembles that of the carbonic acid–bicarbonate buffer system.
  - In the ECF, the phosphate buffer system plays only a supporting role in the regulation of pH. The phosphate buffer system is quite important in buffering the pH of the ICF.

**Maintenance of Acid–Base Balance**

- Although buffer systems can tie up excess H⁺, they provide only a temporary solution to an acid–base imbalance. The hydrogen ions are not eliminated, but merely rendered harmless. For homeostasis to be preserved, the captured must ultimately be either permanently tied up in water molecules, through the removal of carbon dioxide at the lungs, or removed from body fluids, through secretion at the kidneys.
- The underlying problem is that the body’s supply of buffer molecules is limited. Suppose that a buffer molecule prevents a change in pH by binding a hydrogen ion that enters the ECF. That buffer molecule is then tied up, reducing the capacity of the ECF to cope with any additional Eventually, all the buffer molecules are bound to and further pH control becomes impossible. The situation can be resolved only by either removing the from the ECF (thereby freeing the buffer molecules) or replacing the buffer molecules.
- If a buffer provides a hydrogen ion to maintain normal pH, homeostatic conditions will return only when either another hydrogen ion has been obtained or the buffer has been replaced. The maintenance of acid–base balance thus includes balancing gains and losses. This “balancing act” involves coordinating the actions of buffer systems with respiratory mechanisms and renal mechanisms.
- These mechanisms support the buffer systems by (1) secreting or absorbing (2) controlling the excretion of acids and bases, and, when necessary, (3) generating additional buffers. It is the combination of buffer systems and these respiratory and renal mechanisms that maintains body pH within narrow limits.
- Respiratory Compensation Respiratory compensation is a change in the respiratory rate that helps stabilize the pH of the ECF. Respiratory compensation occurs whenever body pH strays outside normal limits. Such compensation is effective because respiratory activity has a direct effect on the carbonic acid–bicarbonate buffer system.
Increasing or decreasing the rate of respiration alters pH by lowering or raising the respiratory exchange ratio. When the respiratory exchange ratio rises, the pH falls, because the addition of drives the carbonic acid–bicarbonate buffer system to the right. When the falls, the pH rises because the removal of drives that buffer system to the left.

**Renal Compensation** Renal compensation is a change in the rates of H⁺ and HCO₃⁻ secretion or reabsorption by the kidneys in response to changes in plasma pH. Under normal conditions, the body generates enough organic and fixed acids to add about 100 mEq of H⁺ to the ECF each day. An equivalent number of hydrogen ions must therefore be excreted in urine to maintain acid–base balance.

- In addition, the kidneys assist the lungs by eliminating any that either enters the renal tubules during filtration or diffuses into the tubular fluid as it travels toward the renal pelvis. Hydrogen ions are secreted into the tubular fluid along the proximal convoluted tubule (PCT), the distal convoluted tubule (DCT), and the collecting system.
- The ability to eliminate a large number of hydrogen ions in a normal volume of urine depends on the presence of buffers in the urine.
- The three major buffers involved are the carbonic acid–bicarbonate buffer system, the phosphate buffer system, and the ammonia buffer system.

The Renal Responses to Acidosis and Alkalosis

Acidosis (low body fluid pH) develops when the normal plasma buffer mechanisms are stressed by excessive numbers of hydrogen ions. The kidney tubules do not distinguish among the various acids that may cause acidosis. Whether the fall in pH results from the production of volatile, fixed, or organic acids, the renal contribution remains limited to (1) the secretion of (2) the activity of buffers in the tubular fluid, (3) the removal of and (4) the reabsorption of NaHCO₃. When alkalosis (high body fluid pH) develops, (1) the rate of secretion at the kidneys declines, (2) tubule cells do not reclaim the bicarbonates in tubular fluid, and (3) the collecting system transports HCO₃⁻ into tubular fluid while releasing a strong acid (HCl) into peritubular fluid.

**Disturbances of Acid–Base Balance, p. 1014**

- When buffering mechanisms are severely stressed, the pH drifts outside these limits, producing symptoms of alkalosis or acidosis. Temporary shifts in the pH of body fluids occur frequently. Rapid and complete recovery involves a combination of buffer system activity and the respiratory and renal responses.
- More serious and prolonged disturbances of acid–base balance can result under the following circumstances:
  - Any Disorder Affecting Circulating Buffers, Respiratory Performance, or Renal Function.
  - Cardiovascular Conditions. Conditions such as heart failure or hypotension can affect the pH of internal fluids by causing fluid shifts and by changing glomerular filtration rates and respiratory efficiency.
  - Conditions Affecting the Central Nervous System. Neural damage or disease that affects the CNS can affect the respiratory and cardiovascular reflexes that are essential to normal pH regulation.
- Serious abnormalities in acid–base balance generally have an initial acute phase, in which the pH moves rapidly out of the normal range. If the condition persists, physiological adjustments occur; the individual then enters the compensated phase. Unless the underlying problem is corrected, compensation cannot be completed, and blood chemistry will remain abnormal. The pH typically remains outside normal limits even after compensation has occurred. Even if the pH is within the normal range, the or concentrations can be abnormal.
- The primary source of the problem is usually indicated by the name given to the resulting condition:
  - Respiratory acid–base disorders result from a mismatch between carbon dioxide generation in peripheral tissues and carbon dioxide excretion at the lungs. When a respiratory acid–base disorder is present, the carbon dioxide level of the ECF is abnormal.
Metabolic acid–base disorders are caused by the generation of organic or fixed acids or by conditions affecting the concentration of in the ECF. Respiratory compensation alone may restore normal acid–base balance in individuals with respiratory acid–base disorders.

Respiratory Acidosis

- **Respiratory acidosis** develops when the respiratory system cannot eliminate all the carbon dioxide generated by peripheral tissues. The primary sign is low plasma pH due to hypercapnia, an elevated plasma $P_{CO_2}$. The usual cause is hypventilation, an abnormally low respiratory rate. Respiratory acidosis is the most common challenge to acid–base equilibrium.

Respiratory Alkalosis

- Problems resulting from respiratory alkalosis are relatively uncommon. Respiratory alkalosis develops when respiratory activity lowers plasma to below normal levels, a condition called hypocapnia. A temporary hypocapnia can be produced by hyperventilation when increased respiratory activity leads to a reduction in the arterial $P_{CO_2}$. Continued hyperventilation can elevate the pH to levels as high as 8.0. This condition generally corrects itself, because the reduction in $P_{CO_2}$ halts the stimulation of the chemoreceptors, so the urge to breathe fades until carbon dioxide levels have returned to normal. Respiratory alkalosis caused by hyperventilation seldom persists long enough to cause a clinical emergency.

Metabolic Acidosis

- **Metabolic acidosis** is the second most common type of acid–base imbalance. It has three major causes:
  - The most widespread cause of metabolic acidosis is the production of a large number of fixed or organic acids. The hydrogen ions released by these acids overload the carbonic acid–bicarbonate buffer system, so pH begins to decline.
    - Lactic acidosis can develop after strenuous exercise or prolonged tissue hypoxia (oxygen starvation) as active cells rely on anaerobic respiration.
    - Ketoacidosis results from the generation of large quantities of ketone bodies during the postabsorptive state of metabolism. Ketoacidosis is a problem in starvation, and a potentially lethal complication of poorly controlled diabetes mellitus.
  - A less common cause of metabolic acidosis is an impaired ability to excrete at the kidneys.
  - Metabolic acidosis occurs after severe bicarbonate loss. The carbonic acid–bicarbonate buffer system relies on bicarbonate ions to balance hydrogen ions that threaten pH balance.
- Combined Respiratory and Metabolic Acidosis Respiratory acidosis and metabolic acidosis are typically linked, because oxygen-starved tissues generate large quantities of lactic acid, and because sustained hypoventilation leads to decreased arterial $P_{O_2}$.

Metabolic Alkalosis

- **Metabolic alkalosis** occurs when $HCO_3^-$ concentrations become elevated. The bicarbonate ions then interact with hydrogen ions in solution, forming $H_2CO_3$. The resulting reduction in $H^+$ concentrations causes symptoms of alkalosis. Metabolic alkalosis is relatively rare.

The Detection of Acidosis and Alkalosis

- Virtually anyone who has a problem that affects the cardiovascular, respiratory, urinary, digestive, or nervous system may develop potentially dangerous acid–base imbalances. For this reason, most diagnostic blood tests include several screens designed to provide information about pH and buffer function. Standard tests monitor blood pH, and levels. These measurements make recognition of acidosis or alkalosis, and the classification of a particular condition as respiratory or metabolic, relatively straightforward.

Aging and Fluid, Electrolyte, and Acid–Base Balance, p. 1019

- Fetuses and infants have very different requirements for the maintenance of fluid, electrolyte, and acid–base balance than do adults. A fetus obtains the water, organic nutrients, and electrolytes it needs from the maternal bloodstream. Buffers in the fetal bloodstream provide short-term pH control, and the maternal kidneys eliminate the generated.
A newborn’s body water content is high: At birth, water accounts for roughly 75 percent of body weight, compared with 50–60 percent in adults. Basic aspects of electrolyte balance are the same in newborns as in adults, but the effects of fluctuations in the diet are much more immediate in newborns because reserves of minerals and energy sources are much smaller.

- Aging affects many aspects of fluid, electrolyte, and acid–base balance, including the following:
  - Total body water content gradually decreases with age. Between ages 40 and 60, average total body water content declines slightly, to 55 percent for males and 47 percent for females. After age 60, the values decline further, to roughly 50 percent for males and 45 percent for females. Among other effects, each decrease reduces the dilution of waste products, toxins, and any drugs that have been administered.
  - A reduction in the glomerular filtration rate and in the number of functional nephrons reduces the body’s ability to regulate pH through renal compensation.
  - The body’s ability to concentrate urine declines, so more water is lost in urine. In addition, the rate of insensible perspiration increases as the skin becomes thinner and more delicate. Maintaining fluid balance therefore requires a higher daily water intake. A reduction in ADH and aldosterone sensitivity makes older people less able than younger people to conserve body water when losses exceed gains.
  - Many people over age 60 experience a net loss in body mineral content as muscle mass and skeletal mass decrease. This loss can be prevented, at least in part, by a combination of exercise and an increased dietary mineral supply.
  - The reduction in vital capacity that accompanies aging reduces the body’s ability to perform respiratory compensation, increasing the risk of respiratory acidosis. This problem can be compounded by arthritis, which can reduce vital capacity by limiting rib movements, and by emphysema, another condition that, to some degree, develops with aging.
  - Disorders affecting major systems become more common with increasing age. Most, if not all, of these disorders have some effect on fluid, electrolyte, and/or acid–base balance.