SECTION I

Cellular & Molecular Basis for Medical Physiology

Study of physiological system structure and function, as well as pathophysiological alterations, has its foundations in physical and chemical laws and the molecular and cellular makeup of each tissue and organ system. *Ganong's Review of Medical Physiology* is structured into seven sections. This first section provides an overview of the basic building blocks or bases that provide the important framework for human physiology. It is important to note here that the seven chapters in this initial section are not meant to provide an exhaustive understanding of biophysics, biochemistry, or cellular and molecular physiology; rather, they are to serve as a reminder of how the basic principles from these disciplines contribute to medical physiology discussed in later sections associated with physiological functions of organs and systems.

In the first two chapters of this section, the following basic building blocks are introduced and discussed: electrolytes; carbohydrates, lipids, and fatty acids; amino acids and proteins; and nucleic acids. Students are reminded of some of the basic principles and building blocks of biophysics and biochemistry and how they fit into the physiologic environment. Examples of direct clinical applications are provided in the clinical boxes to help bridge the gap between basic principles and human cell, tissue, and organ functions. These basic principles are followed up with a discussion of the generic cell and its components. It is important to realize the cell is the basic functional unit within the body, and it is the collection and fine-tuned interactions among and between these fundamental units that allow for proper tissue, organ, and organism function.

In the third to seventh chapters of this introductory section, we take a cellular approach to lay the groundwork for understanding groups of cells that interact with many of the systems discussed in future chapters. The first group of cells presented contribute to inflammatory reactions in the body. These individual players, their coordinated behavior, and the net effects of the "open system" of inflammation in the body are discussed in detail. The second group of cells discussed are responsible for the excitatory responses in human physiological function and include both neuronal and muscle cells. A fundamental understanding of the inner workings of these cells, and how they are controlled by their neighboring cells, helps the student to understand their eventual integration into individual systems discussed in later sections.

This first section serves as an introduction, refresher, and quick source of material to best understand organ functions and systems physiology presented in the later sections. For detailed understanding of any of the chapters within this section, several excellent and current textbooks that provide more in-depth reviews of principles of biochemistry, biophysics, cell physiology, and muscle and neuronal physiology are provided as resources at the end of each individual chapter. Students are encouraged to visit these texts for a more thorough understanding of these basic principles.

General Principles & Energy Production in Medical Physiology

CHAPTER 1

OBJECTIVES

After studying this chapter, you should be able to:

- Define functional units used in measuring physiological properties.
- Define pH and buffering.
- Understand electrolytes and define diffusion, osmosis, and tonicity.
- Define and explain the significance of resting membrane potential.
- Understand in general terms the basic building blocks of the cell (eg, nucleotides, amino acids, carbohydrates, and fatty acids) to cell metabolism, proliferation, and function.
- Understand higher-order structures of the basic building blocks of the cell (eg, DNA, RNA, proteins, and lipids) to cell replication, proliferation, and signal transduction.
- Understand the basic contributions of the basic building blocks of the cell to its structure, function, and energy balance.

INTRODUCTION

In unicellular organisms, all vital processes occur in a single cell. As the evolution of multicellular organisms progressed, various cell groups organized into tissues, and organs have taken over particular functions. In humans and other vertebrate animals, there are a number of specialized collections of cells that consist in organ systems serving for different functions. For example, a gastrointestinal system to digest and absorb food; a respiratory system to take up O_2 and eliminate CO_2; a urinary system to remove wastes; a cardiovascular system to distribute nutrients, O_2, and the products of metabolism; a reproductive system to perpetuate the species; and nervous and endocrine systems to coordinate and integrate the functions of the other systems. This book is concerned with the way these systems function and the way each contributes to the functions of the body as a whole. This first chapter lays a foundation for the discussion of these organ systems with a review of basic biophysical and biochemical principles at the cellular level and the introduction of the molecular building blocks that contribute to cell physiological function within these organ systems.

GENERAL PRINCIPLES

THE BODY AS ORGANIZED "SOLUTIONS"

In the average young adult male, 18% of the body weight is protein and related substances, 7% is mineral, and 15% is fat. The remaining 60% is water. The distribution of the body water is shown in **Figure 1–1A**.

The cells that make up the bodies of all but the simplest multicellular animals, both aquatic and terrestrial, exist in an "internal sea" of **extracellular fluid (ECF)** enclosed within the integument of the animal. From this fluid, the cells take up O_2 and nutrients; into it, they discharge metabolic waste products. The ECF is more dilute than present-day seawater, but its composition closely resembles that of the primordial oceans in which, presumably, all life originated.

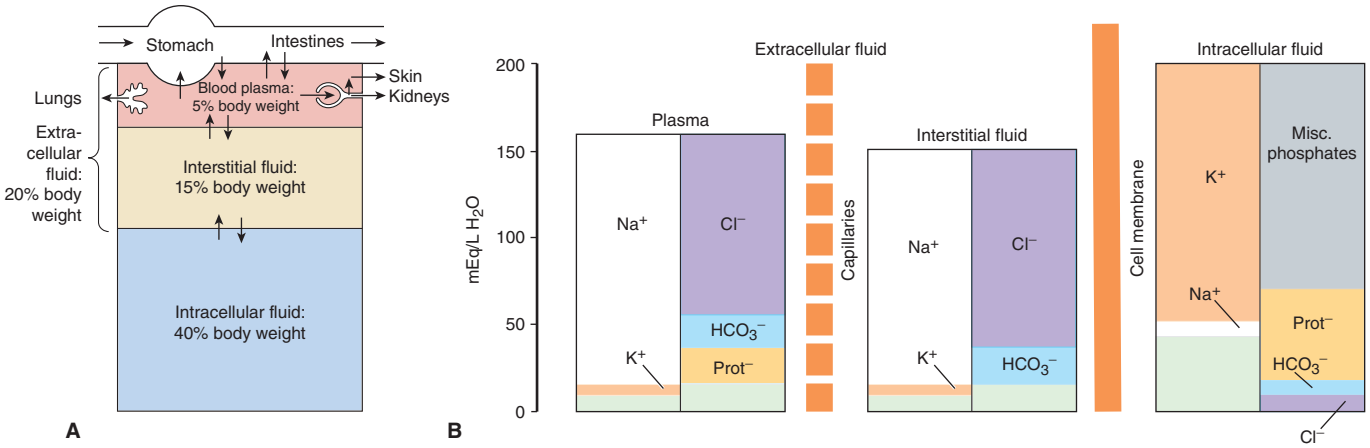


FIGURE 1–1 Organization of body fluids and electrolytes into compartments. A) Body fluids can be divided into intracellular and extracellular fluid compartments (ICF and ECF, respectively). Their contribution to percentage body weight (based on a healthy young adult male; slight variations exist with age and gender) emphasizes the dominance of fluid makeup of the body. Transcellular fluids, which constitute a very small percentage of total body fluids, are not shown. Arrows represent fluid movement between compartments. **B)** Electrolytes and proteins are unequally distributed among the body fluids. This uneven distribution is crucial to physiology. $Prot^-$, protein, which tends to have a negative charge at physiologic pH.

In animals with a closed vascular system, the ECF is divided into the **interstitial fluid,** the circulating **blood plasma,** and **the lymph fluid that bridges these two domains.** The interstitial fluid is the part of the ECF that is outside the vascular and lymph systems, bathing the cells. The plasma and the cellular elements of the blood, principally red blood cells, fill the vascular system, and together they constitute the **total blood volume.** About one-third of the **total body water** is extracellular; the remaining two-thirds is intracellular **(intracellular fluid).** Inappropriate compartmentalization of the body fluids can result in edema **(Clinical Box 1–1) (Clinical Concept Check 1–1)**.

CLINICAL BOX 1–1

Edema

Edema is the buildup of body fluids extracellularly or interstitially in tissues. The increased fluid is related to an increased leak from the blood and/or reduced removal by the lymph system. Edema is often observed in the feet, ankles, and legs, but can happen in many areas of the body in response to disease, including those of the heart, lung, liver, kidney, or thyroid.

THERAPEUTIC HIGHLIGHTS

The best treatment for edema includes reversing the underlying disorder. Thus, proper diagnosis of the cause of edema is the primary first step in therapy. More general treatments include restricting dietary sodium to minimize fluid retention and using appropriate diuretic therapy.

CLINICAL CONCEPT CHECK 1–1

A 35-year-old woman went to see her primary doctor with a complaint of swelling of the skin in her ankles and feet. It often started after walking about in the neighborhood or in a shopping mall, standing or sitting in a chair for a long time. Recently, the patient experienced pain in her leg and had difficulty breathing. After physical and ultrasound examinations, the doctor ordered a blood test and a CT angiogram for her. Then, the doctor explained to her that she might have a blood clot from her leg that travels to her lung. What is the likely diagnosis and what is the treatment for her?

The intracellular component of the body water accounts for about 40% of body weight and the extracellular component for about 20%. Approximately 25% of the extracellular component is in the vascular system (plasma = 5% of body weight) and 75% outside the blood vessels (interstitial fluid = 15% of body weight). The total blood volume is about 8% of body weight. Flow between these compartments is tightly regulated.

UNITS FOR MEASURING CONCENTRATION OF SOLUTES

In considering the effects of various physiologically important substances and the interactions among them, the number of molecules, electrical charges, or particles of a substance per unit volume of a particular body fluid are often more meaningful than simply the weight of the substance per unit volume. For this reason, physiological concentrations are frequently expressed in moles, equivalents, or osmoles.

Moles

A mole is the gram-molecular weight of a substance, that is, the molecular weight (MW) of the substance in grams. Each mole (mol) consists of 6×10^{23} molecules. The millimole (mmol) is 1/1000 of a mole, and the micromole (μmol) is 1/1,000,000 of a mole. Thus, 1 mol of NaCl = 23 g + 35.5 g = 58.5 g and 1 mmol = 58.5 mg. The mole is the standard unit for expressing the amount of substances in the SI unit system.

The molecular weight of a substance is the ratio of the mass of one molecule of the substance to the mass of one-twelfth the mass of an atom of carbon-12. Because molecular weight is a ratio, it is dimensionless. The dalton (Da) is a unit of mass equal to one-twelfth the mass of an atom of carbon-12. The kilodalton (1 kDa = 1000 Da) is a useful unit for expressing the molecular mass of proteins. Thus, for example, one can speak of a 64-kDa protein or state that the **molecular mass** of the protein is 64,000 Da. However, because molecular weight is a dimensionless ratio, it is incorrect to say that the molecular weight of the protein is 64 kDa.

Equivalents

The concept of electrical equivalence is important in physiology because many of the solutes in the body are in the form of charged particles. One equivalent (Eq) is 1 mol of an ionized substance divided by its valence. One mole of NaCl dissociates into 1 Eq of Na^+ and 1 Eq of Cl^-. One equivalent of Na^+ = 23 g, but 1 Eq of Ca^{2+} = 40 g ÷ 2 = 20 g. The milliequivalent (mEq) is 1/1000 of 1 Eq.

Electrical equivalence is not necessarily the same as chemical equivalence. A gram equivalent is the weight of a substance that is chemically equivalent to 8.0 g of oxygen. The normality (N) of a solution is the number of gram equivalents in 1 liter (L). A 1 N solution of hydrochloric acid (HCl) contains both H^+ (1.0 g) and Cl^- (35.5 g) equivalents, = (1.0 g + 35.5 g)/L = 36.5 g/L.

WATER, ELECTROLYTES, & ACID/BASE

The water molecule (H_2O) is an ideal solvent for physiological reactions. H_2O has a **dipole moment** where oxygen slightly pulls away electrons from the hydrogen atoms and creates a charge separation that makes the molecule **polar.** This allows water to dissolve a variety of charged atoms and molecules. It also allows the H_2O molecule to interact with other H_2O molecules via hydrogen bonding. The resulting hydrogen bond network in water allows for several key properties relevant to physiology: (1) water has a high surface tension, (2) water has a high heat of vaporization and heat capacity, and (3) water has a high dielectric constant. In layman's terms, H_2O is an excellent biological fluid that serves as a solute; it provides optimal heat transfer and conduction of current.

Electrolytes (eg, NaCl) are molecules that dissociate in water to their cation (Na^+) and anion (Cl^-) equivalents. Because of the net charge on water molecules, these electrolytes tend not to reassociate in water. There are many important electrolytes in physiology, notably Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, and HCO_3^-. It is important to note that electrolytes and other charged compounds (eg, proteins) are unevenly distributed in the body fluids **(Figure 1–1B)**. These separations play an important role in physiology, for example, in the establishment of membrane potential and generation of action potential.

pH & BUFFERING

The maintenance of a stable hydrogen ion concentration ($[H^+]$) in body fluids is essential to life. The **pH** of a solution is defined as the logarithm to the base 10 of the reciprocal of the H^+, that is, the negative logarithm of the $[H^+]$. The pH of water at 25°C, in which H^+ and OH^- ions are present in equal numbers, is 7.0 **(Figure 1–2)**. For each pH unit less than 7.0, the $[H^+]$ is increased 10-fold; for each pH unit above 7.0, it is decreased 10-fold. In the plasma of healthy individuals, pH is slightly alkaline, maintained in the narrow range of 7.35–7.45 **(Clinical Box 1–2)**. Conversely, gastric fluid pH can be quite acidic (on the order of 3.0) and pancreatic secretions can be quite alkaline (on the order of 8.0). Enzymatic activity and protein structure are frequently sensitive to pH; in any given body or cellular compartment, pH is maintained to allow for maximal enzyme/protein efficiency.

Molecules that act as H^+ donors in solution are considered acids, while those that tend to remove H^+ from solutions are considered bases. Strong acids (eg, HCl) or bases (eg, NaOH) dissociate completely in water and thus can most change the $[H^+]$ in solution. In physiological compounds, most acids or bases are considered "weak," that is, they contribute or remove relatively few H^+ from the solution. Body pH is stabilized by the **buffering capacity** of the body fluids. A **buffer** is a substance that has the ability to bind or release H^+ in solution, thus keeping the pH of the solution relatively

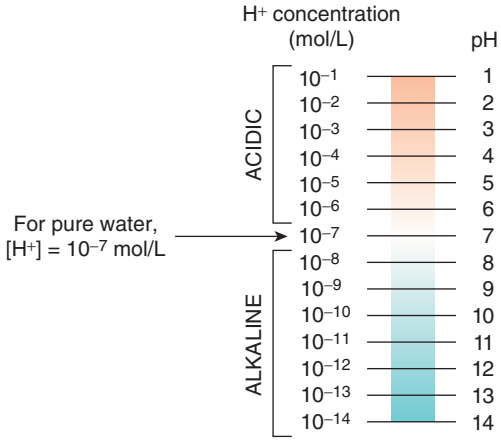


FIGURE 1–2 Proton concentration and pH. Relative proton (H^+) concentrations for solutions on a pH scale are shown.

CLINICAL BOX 1–2

Acid–Base Balance and Disorders

Excesses of acid (acidosis) or base (alkalosis) exist when the blood or blood plasma is outside the normal pH range (7.35–7.45). Such changes impair the delivery of O_2 to and removal of CO_2 from tissues. There are a variety of conditions and diseases that can interfere with pH control in the body and cause blood pH to fall outside of healthy limits. Acid–base disorders that result from respiration to alter CO_2 concentration are called respiratory acidosis and respiratory alkalosis. Respiratory acidosis is often caused by respiratory failure or ventilator failure, while respiratory alkalosis is caused by alveolar hyperventilation and often found in patients with chronic liver disease. Nonrespiratory disorders that affect HCO_3^- concentration are referred to as metabolic acidosis and metabolic alkalosis. Metabolic acidosis or alkalosis can be caused by electrolyte disturbances, severe vomiting or diarrhea, ingestion of certain drugs and toxins, kidney disease, and diseases that affect normal metabolism (eg, diabetes).

THERAPEUTIC HIGHLIGHTS

Proper treatments for acid–base disorders are dependent on correctly identifying the underlying causal process(es). This is especially true when mixed disorders are encountered. Treatment of respiratory acidosis should be initially targeted at restoring ventilation, whereas treatment for respiratory alkalosis is focused on the reversal of the primary causes (eg, alveolar hyperventilation associated with head injury and anxiety, hypoxemia due to peripheral chemoreceptor stimulation, pulmonary embolism, and edema). Bicarbonate (via intravenous injection) is typically used as a treatment for acute metabolic acidosis. An adequate amount of a chloride salt can restore acid–base balance to normal over a matter of days for patients with a chloride-responsive metabolic alkalosis whereas chloride-resistant metabolic alkalosis requires treatment of the underlying disease.

constant despite the addition of considerable quantities of acid or base. Of course, there are a number of buffers at work in biological fluids at any given time. All buffer pairs in a homogenous solution are in equilibrium with the same $[H^+]$; this is known as the **isohydric principle.** One outcome of this principle is that by assaying a single buffer system, we can understand a great deal about all of the biological buffers in that system.

When acids are placed into solution, there is dissociation of some of the component acid (HA) into its proton (H^+) and free acid (A^-). This is frequently written as an equation:

$$HA \rightleftharpoons H^+ + A^-$$

According to the laws of mass action, a relationship for the dissociation can be defined mathematically as:

$$K_a = [H^+][A^-]/[HA]$$

where K_a is a constant, and the brackets represent concentrations of the individual species (elements). In layman's terms, the product of the proton concentration ($[H^+]$) and the free acid concentration ($[A^-]$) divided by the bound acid concentration ([HA]) is a defined constant (K). This can be rearranged to read:

$$[H^+] = K_a\,[HA]/[A^-]$$

If the logarithm of each side is taken:

$$\log[H^+] = \log K_a + \log[HA]/[A^-]$$

Both sides can be multiplied by –1 to yield:

$$-\log[H^+] = -\log K_a + \log[A^-]/[HA]$$

This can be written in a more conventional form known as the **Henderson–Hasselbalch equation:**

$$pH = pK_a + \log[A^-]/[HA]$$

This relatively simple equation is quite powerful. One thing that can be discerned right away is that the buffering capacity of a particular weak acid is best when the pK_a of that acid is equal to the pH of the solution, or when:

$$[A^-] = [HA],\ pH = pK_a$$

Similar equations can be set up for weak bases. An important buffer in the body is carbonic acid (H_2CO_3). Carbonic acid is a weak acid, and thus is only partly dissociated into H^+ and HCO_3^-:

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

If H^+ is added to a solution of carbonic acid, the equilibrium shifts to the left and most of the added H^+ is removed from the solution. If OH^- is added, H^+ and OH^- combine, taking H^+ out of the solution. However, the decrease is countered by more dissociation of H_2CO_3, and the decline in H^+ concentration is minimized. A unique feature of HCO_3^- is the linkage between its buffering ability and the ability for the lungs to remove CO_2 from the body. Other important biological buffers include phosphates and proteins.

DIFFUSION

The particles (molecules or atoms) of a substance dissolved in a solvent are in continuous random movement. Diffusion is the process by which a gas or a substance in a solution expands or moves from one region to another, because of the motion of its particles, to fill all the available volume. A given particle is equally likely to move into or out of an area in which it is present in high concentration. However, because there are more particles in the area of high concentration, the total number of particles moving to areas of lower concentration is greater; that is, there is a **net flux** of solute particles from areas of high concentration to areas of low concentration. The time required for equilibrium by diffusion is proportional to the square of the diffusion distance. The magnitude of the diffusing tendency from one region to another separated by a boundary (eg, cell membrane, blood-gas barrier) is directly proportional to the cross-sectional area across which diffusion is taking place and the **concentration gradient,** or **chemical gradient,** which is the difference in concentration of the diffusing substance divided by the thickness of the boundary **(Fick's law of diffusion).** Thus,

$$J = -DA\frac{\Delta c}{\Delta x}$$

where J is the net rate of diffusion, D is the diffusion coefficient, A is the area, and $\Delta c/\Delta x$ is the concentration gradient. The minus sign indicates the direction of diffusion. When considering movement of molecules from a higher to a lower concentration, $\Delta c/\Delta x$ is negative, so multiplying by –DA gives a positive value. The permeabilities of the boundaries across which diffusion occurs in the body vary, but diffusion is still a major force affecting the distribution of water and solutes.

OSMOSIS

When a substance is dissolved in water, the concentration of water molecules in the solution is less than that in pure water, because the addition of solute to water results in a solution that occupies a greater volume than does the water alone. If the solution is placed on one side of a membrane that is permeable to water but not to the solute, and an equal volume of water is placed on the other, water molecules diffuse down their concentration (chemical) gradient into the solution **(Figure 1–3)**. This process—the diffusion of **solvent** molecules into a region in which there is a higher concentration of a **solute** to which the membrane is impermeable—is called **osmosis.** It is an important factor in physiological processes. The tendency for movement of solvent molecules to a region of greater solute concentration can be prevented by applying pressure to the more concentrated solution. The pressure necessary to prevent solvent migration is the **osmotic pressure** of the solution.

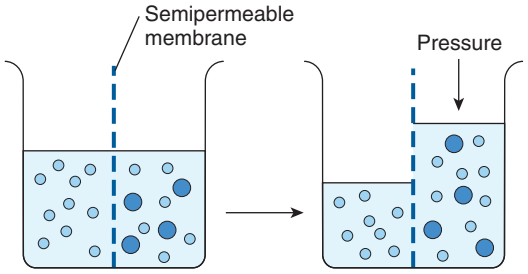


FIGURE 1–3 Diagrammatic representation of osmosis. Water molecules are represented by small open circles, and solute molecules by large solid circles. In the diagram on the left, water is placed on one side of a membrane permeable to water but not to solute, and an equal volume of a solution of the solute is placed on the other. Water molecules move down their concentration (chemical) gradient into the solution, and as shown in the diagram on the right, the volume of the solution increases. As indicated by the arrow on the right, the osmotic pressure is the pressure that would have to be applied to prevent the movement of the water molecules.

Osmotic pressure—like vapor pressure lowering, freezing-point depression, and boiling-point elevation—depends on the number rather than the type of particles in a solution; that is, it is a fundamental colligative property of solutions. In an **ideal solution,** osmotic pressure (P) is related to temperature and volume in the same way as the pressure of a gas:

$$P = \frac{nRT}{V}$$

where n is the number of particles, R is the gas constant, T is the absolute temperature, and V is the volume. If T is held constant, it is clear that the osmotic pressure is proportional to the number of particles in solution per unit volume of solution. For this reason, the concentration of osmotically active particles is usually expressed in **osmoles.** One osmole (Osm) equals the gram-molecular weight of a substance divided by the number of freely moving particles that each molecule liberates in solution. For biological solutions, the milliosmole (mOsm; 1/1000 of 1 Osm) is more commonly used.

If a solute is a nonionizing compound such as glucose, the osmotic pressure is a function of the number of glucose molecules present. If the solute ionizes and forms an ideal solution, each ion is an osmotically active particle. For example, NaCl would dissociate into Na^+ and Cl^- ions, so that each mole in solution would supply 2 Osm. One mole of Na_2SO_4 would dissociate into Na^+, Na^+, and SO_4^{2-} supplying 3 Osm. However, the body fluids are not ideal solutions, and although the dissociation of strong electrolytes is complete, the number of particles free to exert an osmotic effect is reduced owing to interactions between the ions. Thus, it is actually the effective concentration **(activity)** in the body fluids rather than the number of equivalents of an electrolyte in solution that determines its osmotic capacity. This is why, for example,

1 mmol of NaCl per liter in the body fluids contributes somewhat less than 2 mOsm of osmotically active particles per liter. The more concentrated the solution, the greater the deviation from an ideal solution.

The osmolal concentration of a substance in a fluid is measured by the degree to which it depresses the freezing point, with 1 mol of an ideal solution depressing the freezing point by 1.86°C. The number of milliosmoles per liter in a solution equals the freezing point depression divided by 0.00186. The **osmolarity** is the number of osmoles per liter of solution (eg, plasma), whereas the **osmolality** is the number of osmoles per kilogram of solvent. Therefore, osmolarity is affected by the volume of the various solutes in the solution and the temperature, while the osmolality is not. Osmotically active substances in the body are dissolved in water, and the density of water is 1, so osmolal concentrations can be expressed as osmoles per liter (Osm/L) of water. In this book, osmolal (rather than osmolar) concentrations are considered, and osmolality is expressed in milliosmoles per liter (of water); 1 kilogram (kg) of water equals 1 liter (L) given its density of 1 kg/L.

Note that although a homogeneous solution contains osmotically active particles and can be said to have an osmotic pressure, it can exert an osmotic pressure only when it is in contact with another solution across a membrane permeable to the solvent but not to the solute.

OSMOLAL CONCENTRATION OF PLASMA: TONICITY

The freezing point of normal human plasma averages −0.54°C, which corresponds to an osmolal concentration in plasma of 290 mOsm/L. This is equivalent to an osmotic pressure against pure water of 7.3 atmospheres (atm). The osmolality might be expected to be higher than 290 mOsm/L, because the sum of all the cation and anion equivalents in plasma is over 300 mOsm/L. It is not this high because plasma is not an ideal solution and ionic interactions reduce the number of particles free to exert an osmotic effect. Except when there has been insufficient time after a sudden change in composition for equilibrium to occur, all fluid compartments of the body are in (or nearly in) osmotic equilibrium. The term **tonicity** is used to describe the osmolality of a solution relative to plasma. Solutions that have the same osmolality as plasma are said to be **isotonic;** those with greater osmolality are **hypertonic;** and those with lesser osmolality are **hypotonic.** All solutions that are initially isosmotic with plasma (ie, that have the same actual osmotic pressure or freezing-point depression as plasma) would remain isotonic if it were not for the fact that some solutes diffuse into cells and others are metabolized. Thus, a 0.9% saline solution remains isotonic because there is no net movement of the osmotically active particles in the solution into cells and the particles are not metabolized. On the other hand, a 5% glucose solution is isotonic when initially infused intravenously, but glucose is metabolized, so the net effect is that of infusing a hypotonic solution.

It is important to note the relative contributions of the various plasma components to the total osmolal concentration of plasma. All but about 20 of the 290 mOsm in each liter of normal plasma are contributed by Na^+ and its accompanying anions, principally Cl^- and HCO_3^-. Other cations and anions make a relatively small contribution. Although the concentration of the plasma proteins is large when expressed in grams per liter, they normally contribute less than 2 mOsm/L because of their very high molecular weights. The major nonelectrolytes of plasma are glucose and urea, which in the steady state are in equilibrium with cells. Their contributions to osmolality are normally about 5 mOsm/L each but can become quite large in hyperglycemia or uremia. The total plasma osmolality is important in assessing dehydration, overhydration, and other fluid and electrolyte abnormalities **(Clinical Box 1–3) (Clinical Concept Check 1–3)**.

NONIONIC DIFFUSION

Some weak acids and bases are quite soluble in cell membranes in the undissociated form, whereas they cannot cross membranes in the charged (ie, dissociated) form. Consequently, if molecules of the undissociated substance diffuse from one side of the membrane to the other and then dissociate, there is appreciable net movement of the undissociated substance from one side of the membrane to the other. This phenomenon is called **nonionic diffusion.**

DONNAN EFFECT

When an ion on one side of a membrane cannot diffuse through the membrane, the distribution of other ions to which the membrane is permeable is affected in a predictable way. For example, the negative charge of a nondiffusible anion hinders diffusion of the diffusible cations and favors diffusion of the diffusible anions. Consider the situation shown in **Figure 1–4**, in which the membrane (M) between compartment X and compartment Y is impermeable to charged proteins ($Prot^-$) but freely permeable to K^+ and Cl^-.

Assume that the concentrations of the anions (eg, Cl^-) and of the cations (eg, K^+) on the two sides are initially equal. Cl^- diffuses down its concentration gradient from Y to X, and some K^+ moves with the negatively charged Cl^- because of its opposite charge. Therefore,

$$[K^+_X] > [K^+_Y]$$

Furthermore,

$$[K^+_X] + [Cl^-_X] + [Prot^-_X] > [K^+_Y] + [Cl^-_Y]$$

that is, more osmotically active particles are on side X (or compartment X) than on side Y (or compartment Y).

CLINICAL BOX 1–3

Plasma Osmolarity & Disease

Unlike plant cells, which have rigid walls, animal cell membranes are flexible. Therefore, animal cells swell when exposed to extracellular hypotonicity and shrink when exposed to extracellular hypertonicity. Cells contain ion channels and pumps that can be activated to offset moderate changes in osmolarity; however, these can be overwhelmed under certain pathological conditions. Hyperosmolality can cause coma (hyperosmolar coma), a prolonged state of deep unconsciousness. Because of the predominant role of the major solutes and the deviation of plasma from an ideal solution, one can ordinarily approximate the plasma osmolarity within a few mOsm/L by using the following formula, in which the constants convert the clinical units to millimoles of solute per liter:

$$\text{Osmolarity (mOsm/L)} = 2[Na^+]\ \text{(mEq/L)} + 0.055[\text{Glucose}]\ \text{(mg/dL)} + 0.36[\text{BUN}]\ \text{(mg/dL)}$$

BUN is the blood urea nitrogen. The formula is also useful in calling attention to abnormally high concentrations of other solutes. An observed plasma osmolarity (measured by freezing-point depression) that greatly exceeds the value predicted by this formula indicates the presence of a foreign substance such as ethanol, mannitol (sometimes injected to shrink swollen cells osmotically), or poisons such as ethylene glycol (component of antifreeze) or methanol (alternative automotive fuel).

THERAPEUTIC HIGHLIGHTS

Hyperosmolar coma, also referred to as hyperosmolar hyperglycemic syndrome, is characterized by severe hyperglycemia, hyperosmolality, and dehydration without significant ketoacidosis. Hyperosmolar coma and diabetic ketoacidosis are serious complications of diabetes resulting from insulin deficiency and increased glucagon, catecholamines, cortisol, and growth hormone. The treatment is aimed primarily at fluid resuscitation (adequate intravenous access) and replacement (repleting electrolytes and minerals), and retaining euglycemia (insulin therapy). Additionally, mental status and volume status should be assessed and improved for patients with hyperosmolar coma.

CLINICAL CONCEPT CHECK 1–3

Mr. Smith, a 60-year-old construction worker, was rushed to the emergency room (ER) of a local hospital without consciousness. The patient's relatives told the ER doctor that Mr. Smith has had diabetes for many years and recently has not taken his medications because of busy work and travel. A quick test showed that the patient had a very high level of blood sugar. After further examinations, the doctor suspects that Mr. Smith may have hyperosmolar coma. Based on the knowledge you have learned so far, what are the likely blood tests the doctor should have done for the patient in order to make the diagnosis?

Donnan and Gibbs showed that in the presence of a nondiffusible ion, the diffusible ions distribute themselves so that at equilibrium their concentration ratios are equal:

$$\frac{[K^+_X]}{[K^+_Y]} = \frac{[Cl^-_Y]}{[Cl^-_X]}$$

Cross-multiplying,

$$[K^+_X][Cl^-_X] = [K^+_Y][Cl^-_Y]$$

This is the **Gibbs–Donnan equation.** It holds for any pair of cations and anions of the same valence.

The Donnan effect on the distribution of ions has three effects in the body introduced here and discussed below. First, because of charged proteins ($Prot^-$) in cells, there are more osmotically active particles in cells than in interstitial or intercellular fluid, and because animal cells have flexible walls, osmosis would make them swell and eventually rupture if it were not for the sodium-potassium adenosine triphosphatase (**Na, K ATPase)** pumping ions back out of cells. Thus, normal cell volume and pressure largely depend on Na, K ATPase, also known as the Na^+/K^+ pump. Second, because at equilibrium the distribution of permeant ions across the membrane (m, in the example shown in Figure 1–4) is asymmetric, an electrical difference exists across the membrane whose magnitude can be determined by the **Nernst equation** (see below). In the example used here (Figure 1–4), side X will be negative relative to side Y. The charges line up along the membrane, with the concentration gradient for Cl^- exactly balanced by the oppositely directed electrical gradient, and the same holds true for K^+. Third, because there are more proteins in plasma than in interstitial fluid, there is a Donnan effect on ion movement across the capillary wall.

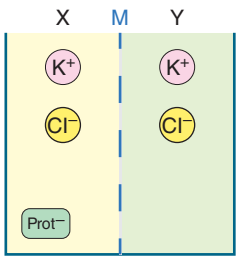


FIGURE 1–4 Equilibrium across a cell membrane. Diagram showing two compartments (X and Y) separated by the membrane (M). Charged K^+ and Cl^- are distributed in both compartments, while charged protein ($prot^-$) is only in X compartment.

FORCES ACTING ON IONS

The forces acting across the cell membrane on each ion can be analyzed mathematically. Chloride ions (Cl^-) are present in higher concentration in the ECF than in the cell interior, and they tend to diffuse along this **concentration gradient** into the cell. The interior of the cell is negative relative to the exterior, and chloride ions are pushed out of the cell along this **electrical gradient.** An equilibrium is reached between Cl^- influx and Cl^- efflux. The membrane potential at which this equilibrium exists is the **equilibrium potential.** Its magnitude can be calculated from the Nernst equation, as follows:

$$E_{Cl} = \frac{RT}{FZ_{Cl}} \ln \frac{[Cl_o^-]}{[Cl_i^-]}$$

where

E_{Cl} = equilibrium potential for Cl^-
R = gas constant
T = absolute temperature
F = the Faraday number (number of coulombs per mole of charge)
Z_{Cl} = valence of Cl^- (−1)
$[Cl_o^-]$ = Cl^- concentration outside the cell
$[Cl_i^-]$ = Cl^- concentration inside the cell

Converting from the natural log to the base 10 log and replacing some of the constants with numeric values holding temperature at 37°C, the equation becomes:

$$E_{Cl} = 61.5 \log \frac{[Cl_i^-]}{[Cl_o^-]} \text{ at } 37^\circ C$$

Note that in converting to the simplified expression the concentration ratio is reversed because the −1 valence of Cl^- has been removed from the expression.

The equilibrium potential for Cl^- (E_{Cl}) in the mammalian spinal neuron, calculated from the standard values listed in Table 1–1, is −70 mV, a value identical to the typical measured resting membrane potential of −70 mV. Therefore, no forces other than those represented by the chemical and electrical gradients need to be invoked to explain the distribution of Cl^- across the membrane.

A similar equilibrium potential can be calculated for K^+ (E_K; again, at 37°C):

$$E_K = \frac{RT}{FZ_K} \ln \frac{[K_o^+]}{[K_i^+]} = 61.5 \log \frac{[K_o^+]}{[K_i^+]} \qquad (\text{at } 37^\circ C)$$

where

E_K = equilibrium potential for K^+
Z_K = valence of K^+ (+1)
$[K_o^+]$ = K^+ concentration outside the cell
$[K_i^+]$ = K^+ concentration inside the cells R, T, and F as above

In this case, the concentration gradient is outward and the electrical gradient inward. In mammalian spinal motor neurons, E_K is −90 mV (Table 1–1). Because the resting membrane potential is −70 mV, there is somewhat more K^+ in the neurons than can be accounted for by the electrical and chemical gradients.

The situation for Na^+ in the mammalian spinal motor neuron is quite different from that for K^+ or Cl^-. The direction of the chemical gradient for Na^+ is inward, to the area where it is in lesser concentration, and the electrical gradient is in the same direction. E_{Na} is +60 mV (Table 1–1). Because neither E_K nor E_{Na} is equal to the membrane potential, one would expect the cell to gradually gain Na^+ and lose K^+ if only passive electrical and chemical forces were acting across the membrane. However, the intracellular concentrations of Na^+ and K^+ remain constant because of selective permeability of the membrane to different ions (Na^+, K^+) and the action of the Na, K ATPase that actively transports Na^+ out of the cell and K^+ into the cell (against their respective electrochemical gradients).

TABLE 1–1 Concentration of some ions inside and outside mammalian spinal motor neurons.

Ion	Concentration (mmol/L of H_2O)		Equilibrium Potential (mV)
	Inside Cell	Outside Cell	
Na^+	15.0	150.0	+60
K^+	150.0	5.5	−90
Cl^-	9.0	125.0	−70

Resting membrane potential = −70 mV.

ESTABLISHMENT OF THE MEMBRANE POTENTIAL

The distribution of ions across the cell membrane and the nature of this membrane provides the explanation for the membrane potential. The concentration gradient for K^+ facilitates its movement out of the cell via K^+ channels, but its electrical gradient is in the opposite (inward) direction. Consequently, an equilibrium is reached in which the tendency of K^+ to move out of the cell is balanced by its tendency to move into the cell, and at that equilibrium there is a slight excess of cations on the outside and anions on the inside. This condition is maintained by Na, K ATPase, which uses the energy of ATP to pump K^+ back into the cell and keeps the intracellular concentration of Na^+ low. Because the Na, K ATPase moves three Na^+ out of the cell for every two K^+ moved in, it also contributes to the membrane potential, and thus is termed an **electrogenic pump.** It should be emphasized that the number of ions responsible for the membrane potential is a minute fraction of

the total number present and that the total concentrations of positive and negative ions are equal everywhere except along the membrane.

ENERGY PRODUCTION

ENERGY TRANSFER

Energy used in cellular processes and cell function is primarily stored in bonds between phosphoric acid residues and certain organic compounds. Because the energy of bond formation in some of these phosphates is particularly high, relatively large amounts of energy (10–12 kcal/mol) are released when the bond is hydrolyzed. Compounds containing such bonds are called **high-energy phosphate compounds.** Not all organic phosphates are of the high-energy type. Many, like glucose 6-phosphate, are low-energy phosphates that on hydrolysis liberate 2–3 kcal/mol. Some of the intermediates formed in carbohydrate metabolism are high-energy phosphates, but the most important energy-rich phosphate compound is **adenosine triphosphate (ATP).** This ubiquitous molecule, ATP **(Figure 1–5),** is the energy storehouse of the body. On hydrolysis to adenosine diphosphate (ADP), it liberates energy directly to such processes as muscle contraction, active transport, and the synthesis of many chemical compounds. Loss of another phosphate to form adenosine monophosphate (AMP) releases more energy.

Another group of energy-rich, or high-energy, compounds are the thioesters, the acyl derivatives of mercaptans. **Coenzyme A (CoA)** is a widely distributed mercaptan-containing adenine, ribose, pantothenic acid, and thioethanolamine

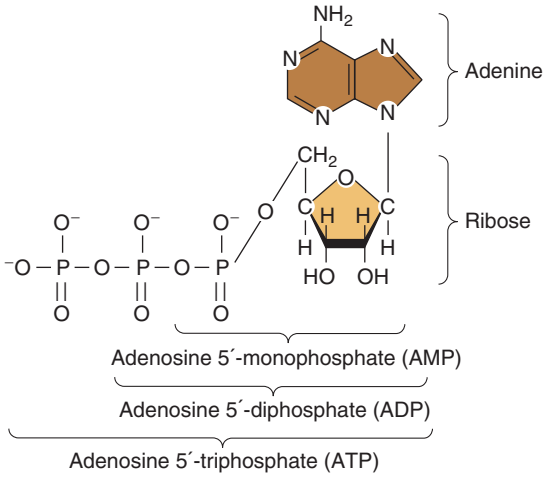


FIGURE 1–5 Energy-rich adenosine derivatives. Adenosine triphosphate is broken down into its backbone purine base and sugar (at right) as well as its high-energy phosphate derivatives (across bottom). (Reproduced with permission from Murray RK, et al: *Harper's Biochemistry*, 28th ed. New York, NY: McGraw-Hill; 2009.)

(Figure 1–6). Reduced CoA (usually abbreviated HS-CoA) reacts with acyl groups (R–CO–) to form R–CO–S–CoA derivatives. A prime example is the reaction of HS-CoA with acetic acid to form acetylcoenzyme A (acetyl-CoA), a compound of pivotal importance in intermediary metabolism. Because acetyl-CoA has a much higher energy content than acetic acid, it combines readily with substances in reactions that would otherwise require outside energy. Acetyl-CoA is therefore often called "active acetate." From the point of view of energetics, formation of 1 mol of any acyl-CoA compound is equivalent to the formation of 1 mol of ATP.

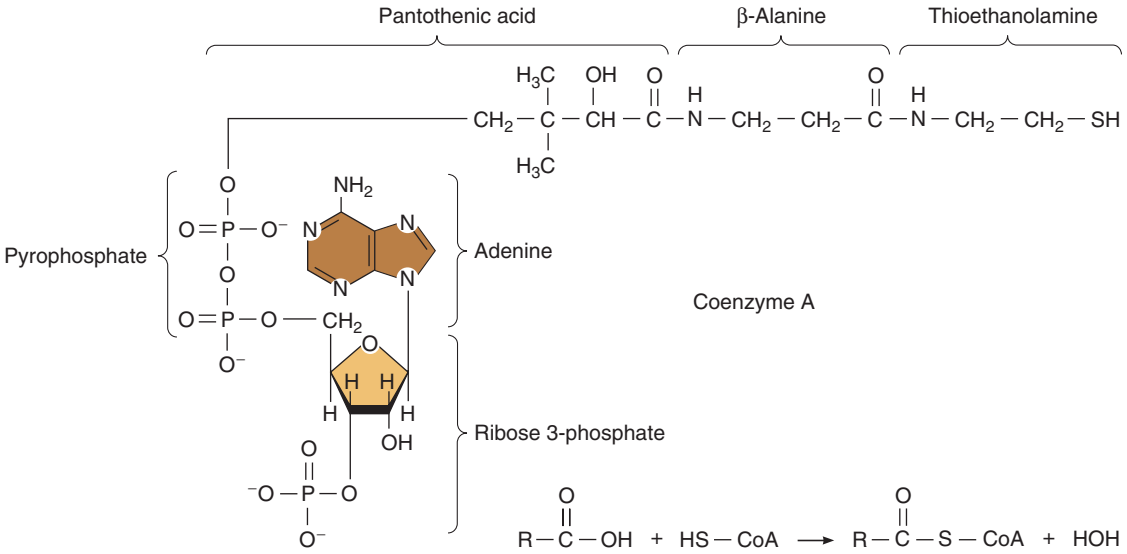


FIGURE 1–6 Coenzyme A (CoA) and its derivatives. Left: Formula of reduced coenzyme A (HS-CoA) with its components highlighted. **Right:** Formula for reaction of CoA with biologically important compounds to form thioesters. R, remainder of molecule.

BIOLOGICAL OXIDATIONS

Oxidation is the combination of a substance with O_2, or loss of hydrogen, or loss of electrons. The corresponding reverse processes are called **reduction.** Biological oxidations are catalyzed by specific enzymes. Cofactors (simple ions) or coenzymes (organic, nonprotein substances) are accessory substances that usually act as carriers for products of the reaction. Unlike the enzymes, the coenzymes may catalyze a variety of reactions.

A number of coenzymes serve as hydrogen acceptors. One common form of biological oxidation is removal of hydrogen from an R–OH group, forming R=O. In such dehydrogenation reactions, nicotinamide adenine dinucleotide (NAD^+) and dihydronicotinamide adenine dinucleotide phosphate ($NADP^+$) pick up hydrogen, forming dihydronicotinamide adenine dinucleotide (NADH) and dihydronicotinamide adenine dinucleotide phosphate (NADPH) **(Figure 1–7)**. The hydrogen is then transferred to the flavoprotein–cytochrome system, reoxidizing the NAD^+ and $NADP^+$. Flavin adenine dinucleotide (FAD) is formed when riboflavin is phosphorylated, forming flavin mononucleotide (FMN). FMN then combines with AMP, forming the dinucleotide. FAD can accept hydrogens in a similar fashion, forming its hydro (FADH) and dihydro ($FADH_2$) derivatives.

The flavoprotein–cytochrome system is a chain of enzymes that transfers hydrogen to oxygen, forming water. This process occurs in the mitochondria. Each enzyme in the chain is reduced and then reoxidized as the hydrogen is passed down the line. Each of the enzymes is a protein with an attached nonprotein prosthetic group. The final enzyme in the chain is cytochrome c oxidase, which transfers hydrogens to O_2, forming H_2O. It contains two atoms of Fe and three of Cu and has 13 subunits.

The principal process by which ATP is formed in the body is **oxidative phosphorylation.** This process harnesses the energy from a proton gradient across the mitochondrial membrane to produce the high-energy bond of ATP (see Figure 2–4 for more detail). Ninety percent of the O_2 consumption, the amount of oxygen used by the body per minute, in the basal state is in mitochondria, and 80% of the mitochondrial O_2 consumption is coupled to ATP synthesis.

ATP is utilized throughout the cell, with the bulk used in a handful of processes: approximately 27% is used for protein synthesis, 24% by Na, K ATPase to help set membrane potential, 9% by gluconeogenesis, 6% by Ca^{2+} ATPase to maintain a low cytosolic Ca^{2+} concentration, 5% by myosin ATPase, and 3% by ureagenesis.

MOLECULAR BUILDING BLOCKS

NUCLEOSIDES, NUCLEOTIDES, & NUCLEIC ACIDS

Nucleosides contain a sugar linked to a nitrogen-containing base. The physiologically important bases, **purines** and **pyrimidines,** have ring structures **(Figure 1–8).** These structures are bound to a sugar, either ribose or 2-deoxyribose, to complete the nucleoside. When inorganic phosphate is added to the nucleoside, a **nucleotide** is formed **(Figure 1–9).** Nucleosides and nucleotides form the backbone for RNA and DNA, as well as a variety of coenzymes and regulatory molecules of physiological

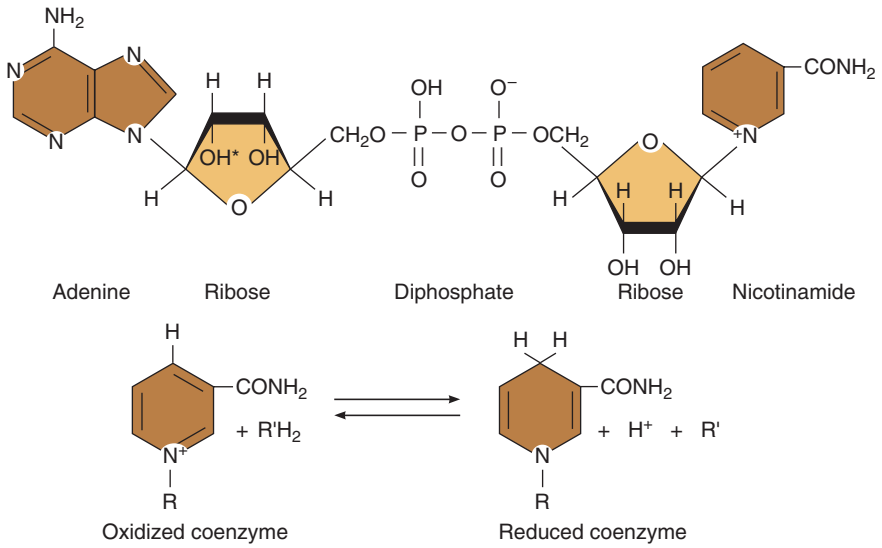
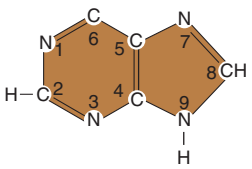
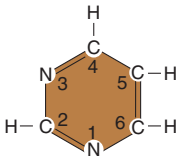


FIGURE 1–7 Structures of molecules important in oxidation–reduction reactions to produce energy. Top: Formula of the oxidized form of nicotinamide adenine dinucleotide (NAD^+). Nicotinamide adenine dinucleotide phosphate ($NADP^+$) has an additional phosphate group at the location marked by the asterisk. **Bottom:** Reaction by which NAD^+ and $NADP^+$ become reduced to form NADH and NADPH. R, remainder of molecule; R′, hydrogen donor.



Adenine: 6-Aminopurine
Guanine: 1-Amino-6-oxypurine
Hypoxanthine: 6-Oxypurine
Xanthine: 2,6-Dioxypurine



Cytosine: 4-Amino-2-oxypyrimidine
Uracil: 2,4-Dioxypyrimidine
Thymine: 5-Methyl-2,4-dioxypyrimidine

FIGURE 1–8 Principal physiologically important purines and pyrimidines. Purine and pyrimidine structures are shown next to representative molecules from each group. Oxypurines and oxypyrimidines may form enol derivatives (hydroxypurines and hydroxypyrimidines) by migration of hydrogen to the oxygen substituents.

importance (eg, NAD^+, $NADP^+$, and ATP) **(Table 1–2).** Nucleic acids in the diet are digested and their constituent purines and pyrimidines absorbed, but most of the purines and pyrimidines are synthesized from amino acids, principally in the liver. The nucleotides and RNA and DNA are then synthesized. RNA is in dynamic equilibrium with the amino acid pool, but DNA, once formed, is metabolically stable throughout life. The purines and pyrimidines released by the breakdown of nucleotides may be reused or catabolized. Minor amounts are excreted unchanged in the urine.

The pyrimidines are catabolized to the **β-amino acids,** β-alanine, and β-aminoisobutyrate. These amino acids have their amino group on β-carbon, rather than the α-carbon typical to physiologically active amino acids. Because β-aminoisobutyrate is a product of thymine degradation, it can serve as a measure of DNA turnover. The β-amino acids are further degraded to CO_2 and NH_3.

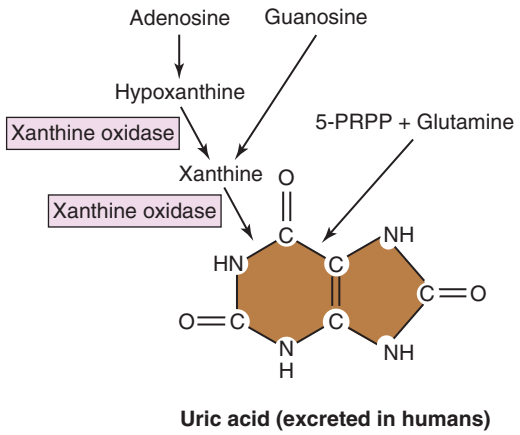


FIGURE 1–9 Synthesis and breakdown of uric acid. Adenosine is converted to hypoxanthine, which is then converted to xanthine, and xanthine is converted to uric acid. The latter two reactions are both catalyzed by xanthine oxidase. Guanosine is converted directly to xanthine, while 5-PRPP and glutamine can be converted to uric acid.

TABLE 1–2 Purine- and pyrimidine-containing compounds.

Type of Compound	Components
Nucleoside	Purine or pyrimidine plus ribose or 2-deoxyribose
Nucleotide (mononucleotide)	Nucleoside plus phosphoric acid residue
Nucleic acid	Many nucleotides forming double-helical structures of two polynucleotide chains
Nucleoprotein	Nucleic acid plus one or more simple basic proteins
Contain ribose	RNA
Contain 2-deoxyribose	DNA

Uric acid is formed by the breakdown of purines and by direct synthesis from 5-phosphoribosyl pyrophosphate (5-PRPP) and glutamine (Figure 1–9). In humans, uric acid is excreted in the urine, but in other mammals, uric acid is further oxidized to allantoin before excretion. The normal blood uric acid level in humans is approximately 4 mg/dL (0.24 mmol/L). In the kidney, uric acid is filtered, reabsorbed, and secreted. Normally, 98% of the filtered uric acid is reabsorbed and the remaining 2% makes up approximately 20% of the amount excreted. The remaining 80% comes from the tubular secretion. The uric acid excretion on a purine-free diet is about 0.5 g/24 h and on a regular diet about 1 g/24 h. Excess uric acid in the blood or urine is a characteristic of gout **(Clinical Box 1–4).**

DNA

DNA is found in bacteria, in the nuclei of eukaryotic cells, and in mitochondria. It is made up of two extremely long nucleotide chains containing the bases adenine (A), guanine (G), thymine (T), and cytosine (C) **(Figure 1–10).** The chains are bound together by hydrogen bonding between the bases, with A bonding to T and G to C. This stable association forms a double-helical structure **(Figure 1–11).** The double helical structure of DNA is compacted in the cell by association with **histones,** and further compacted into **chromosomes.** A diploid human cell contains 46 chromosomes.

A fundamental unit of DNA, or a **gene,** can be defined as the sequence of DNA nucleotides that contain the information for the production of an ordered amino acid sequence for a single polypeptide chain. Interestingly, the protein encoded by a single gene may be subsequently divided into several different physiologically active proteins. Information is accumulating at an accelerating rate about the structure of genes and their regulation. The basic structure of a

CLINICAL BOX 1–4

Gout

Gout is a disease characterized by recurrent attacks of arthritis; urate (a salt derived from uric acid) deposits in the joints, kidneys, and other tissues; and elevated blood and urine uric acid levels. The joint most commonly affected initially is the metatarsophalangeal joint of the great toe. There are two forms of "primary" gout. In one, uric acid production is increased because of various enzyme abnormalities. In the other, there is a selective deficit in renal tubular transport of uric acid. In "secondary" gout, the uric acid levels in the body fluids are elevated as a result of decreased excretion or increased production secondary to some other disease process. For example, excretion is decreased in patients treated with thiazide diuretics and those with renal disease. Production is increased in leukemia and pneumonia because of increased breakdown of uric acid-rich white blood cells.

THERAPEUTIC HIGHLIGHTS

The treatment of gout is aimed at relieving the acute arthritis with drugs such as colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs) and decreasing the uric acid level in the blood. Colchicine does not affect uric acid metabolism, and it apparently relieves gouty attacks by inhibiting the phagocytosis of uric acid crystals by leukocytes, a process that in some way produces the joint symptoms. Phenylbutazone and probenecid inhibit uric acid reabsorption in the renal tubules. Allopurinol, which directly inhibits xanthine oxidase in the purine degradation pathway, is used to decrease uric acid production.

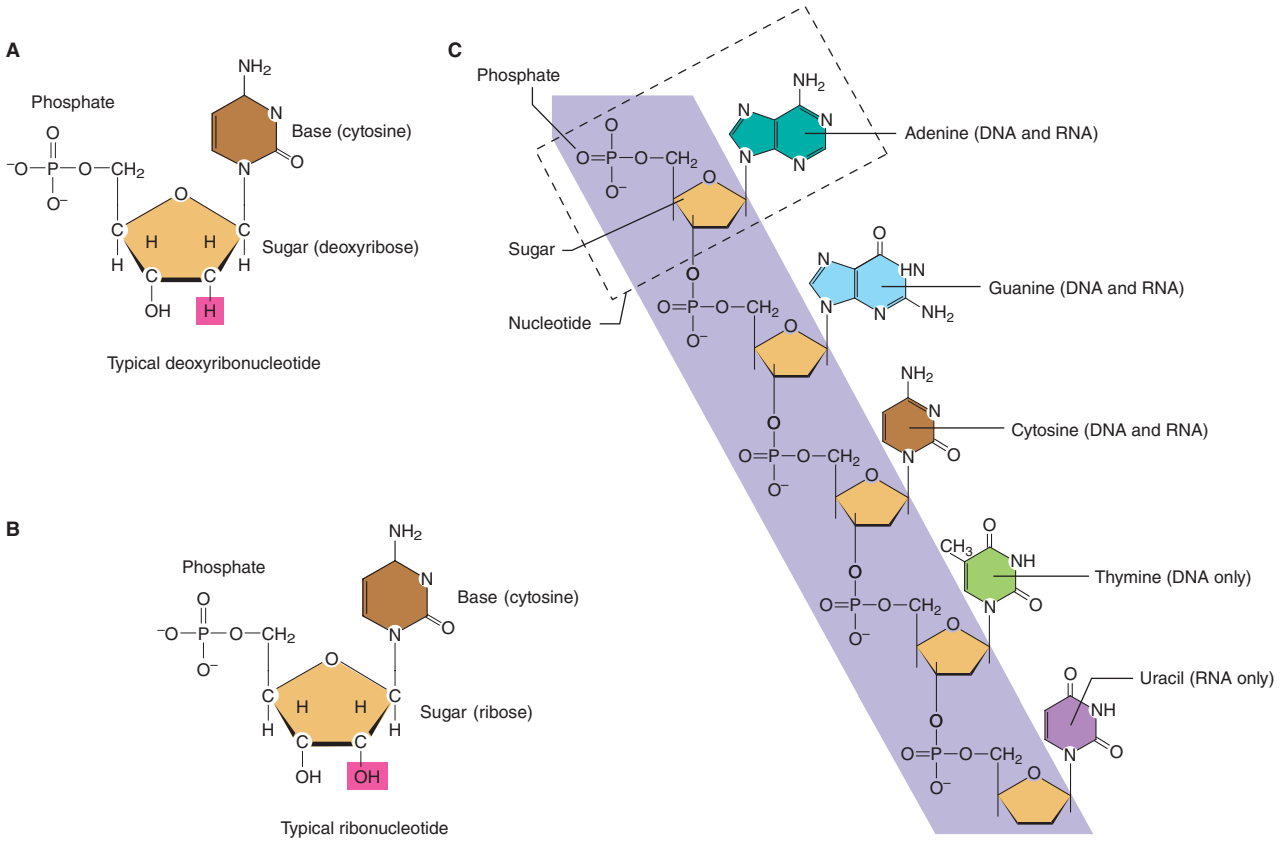


FIGURE 1–10 **Basic structure of nucleotides and nucleic acids. A and B)** The nucleotide cytosine is shown with deoxyribose and with ribose as the principal sugar. **C)** Purine bases adenine and guanine are bound to each other or to pyrimidine bases, cytosine, thymine, or uracil via a phosphodiester backbone between 2′-deoxyribosyl moieties attached to the nucleobases by an N-glycosidic bond. Note that the backbone has a polarity (ie, a 5′ and a 3′ direction). Thymine is only found in DNA, while uracil is only found in RNA.

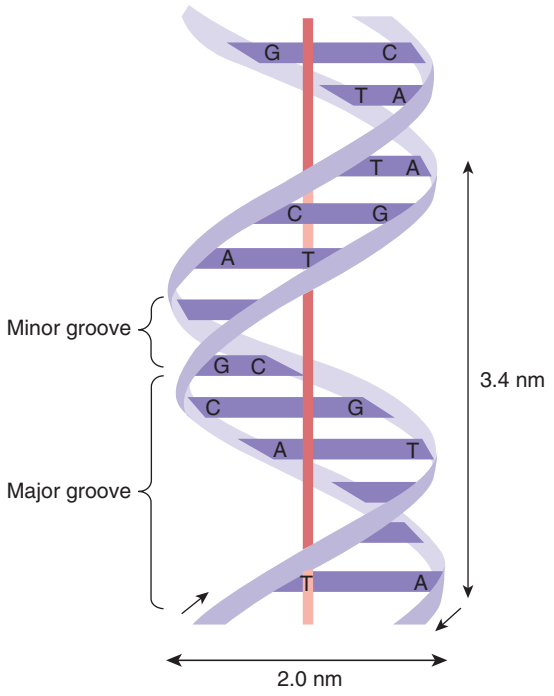


FIGURE 1–11 Double-helical structure of DNA. The compact structure has an approximately 2.0 nm thickness and 3.4 nm between full turns of the helix that contains both major and minor grooves. The structure is maintained in the double helix by hydrogen bonding between purines and pyrimidines across individual strands of DNA. Adenine (A) is bound to thymine (T) and cytosine (C) to guanine (G). (Reproduced with permission from Murray RK et al: *Harper's Biochemistry,* 28th ed. New York, NY: McGraw-Hill; 2009.)

typical eukaryotic gene is shown in diagrammatic form in Figure 1–12. It is made up of a strand of DNA that includes coding and noncoding regions. In eukaryotes, unlike prokaryotes, the portions of the genes that dictate the formation of proteins are usually broken into several segments **(exons)** separated by segments that are not translated **(introns).** Near the transcription start site of the gene is a **promoter,** which is the site at which RNA polymerase and its cofactors bind. It often includes a thymidine–adenine–thymidine–adenine (TATA) sequence **(TATA box),** which ensures that transcription starts at the proper point. Farther out in the 5′ region are **regulatory elements,** which include enhancer and silencer sequences. It has been estimated that each gene has an average of five regulatory sites. Regulatory sequences are sometimes found in the 3′-flanking regions as well. In a diploid cell, each gene will have two **alleles,** or versions of that gene. Each allele occupies the same position on the homologous chromosome. Individual alleles can confer slightly different properties of the gene when fully transcribed. It is interesting to note that changes in single nucleotides within or outside coding regions of a gene **(single nucleotide polymorphisms; SNPs)** can have great consequences for gene function. The study of SNPs in human disease is a growing and exciting area of genetic research.

Gene mutations occur when the base sequence in the DNA is altered from its original sequence. Alterations can be through insertions, deletions, or duplications. Such alterations can affect protein structure and be passed on to daughter cells after cell division. **Point mutations** are single base substitutions. A variety of chemical modifications (eg, alkylating or intercalating agents, or ionizing radiation) can lead to changes in DNA sequences and mutations. The collection of genes within the full expression of DNA from an organism is termed its **genome.** An indication of the complexity of DNA in the human haploid genome (the total genetic message) is its size; it is made up of 3×10^9 base pairs that can code for approximately 30,000 genes. This genetic message is the blueprint for the heritable characteristics of the cell and its descendants. The proteins formed from the DNA blueprint include all the enzymes, and these in turn control the metabolism of the cell.

Each nucleated somatic cell in the body contains the full genetic message, yet there is great differentiation and specialization in the functions of the various types of adult cells. Only small parts of the message are normally transcribed. Thus, the genetic message is normally maintained in a repressed state. However, genes are controlled both spatially and temporally. The double helix requires highly regulated interaction by proteins to unravel for **replication, transcription,** or both.

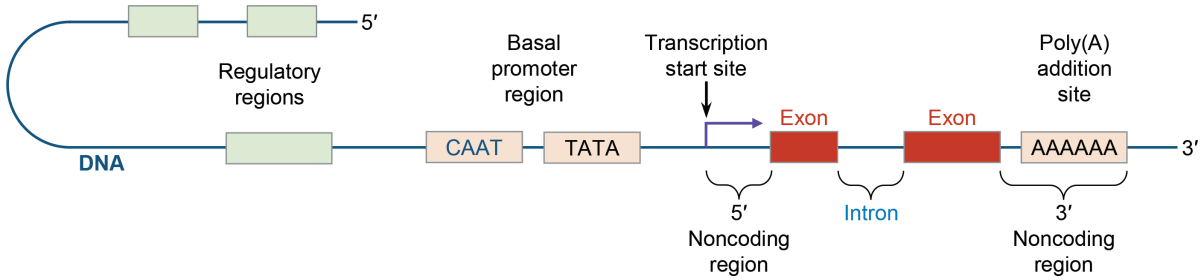


FIGURE 1–12 Diagram of the components of a typical eukaryotic gene. The region that produces introns and exons is flanked by noncoding regions. The 5′-flanking region contains stretches of DNA that interact with proteins to facilitate or inhibit transcription. The 3′-flanking region contains the poly(A) addition site.

REPLICATION: MITOSIS & MEIOSIS

At the time of each somatic cell division **(mitosis),** the two DNA chains separate, each serving as a template for the synthesis of a new complementary chain. DNA polymerase catalyzes this reaction. One of the double helices thus formed goes to one daughter cell and one goes to the other, so the amount of DNA in each daughter cell is the same as that in the parent cell. The life cycle of the cell that begins after mitosis is highly regulated and is termed the **cell cycle** (Figure 1–13). The G_1 (or Gap 1) phase represents a period of cell growth and divides the end of mitosis from the DNA synthesis (or S) phase. Following DNA synthesis, the cell enters another period of cell growth, the G_2 (Gap 2) phase. The ending of this stage is marked by chromosome condensation and the beginning of mitosis (M stage).

In germ cells, reduction division **(meiosis)** takes place during maturation. The net result is that one of each pair of chromosomes ends up in each mature germ cell; consequently, each mature germ cell contains half the amount of chromosomal material found in somatic cells. Therefore, when a sperm unites with an ovum, the resulting zygote has the full complement of DNA, half of which came from the father and half from the mother. The term "ploidy" is sometimes used to refer to the number of chromosomes in cells. Normal resting diploid cells are **euploid** and become **tetraploid** just before division. **Aneuploidy** is the condition in which a cell contains other than the haploid number of chromosomes or an exact multiple of it, and this condition is common in cancerous cells.

RNA

The strands of the DNA double helix not only replicate themselves but also serve as templates by lining up complementary bases for the formation in the nucleus of **RNA.** RNA differs from DNA in that it is single-stranded, has **uracil** (U) in place of thymine (T), and its sugar moiety is ribose rather than 2′-deoxyribose (Figure 1–10). The production of RNA from DNA is called **transcription.** Transcription can lead to several types of RNA including: **messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA),** and other RNAs. Transcription is catalyzed by various forms of **RNA polymerase.**

Typical transcription of an mRNA is shown in **Figure 1–14.** When suitably activated, transcription of the gene into a pre-mRNA starts at the **cap site** and ends about 20 bases beyond the AATAAA sequence. The RNA transcript is capped in the nucleus by addition of 7-methylguanosine triphosphate to the 5′ end; this cap is necessary for proper binding to the ribosome. A **poly(A) tail** of about 100 bases is added to the untranslated segment at the 3′ end to help maintain the stability of the mRNA. The pre-mRNA formed by capping and addition of the poly(A) tail is then processed by elimination of the introns, and once this posttranscriptional modification is complete, the mature mRNA moves to the cytoplasm. Posttranscriptional modification of the pre-mRNA is a regulated process where differential splicing can occur to form more than one mRNA from a single pre-mRNA. The introns of some genes are eliminated by **spliceosomes,** complex units that are made up of small RNAs and proteins. Other introns

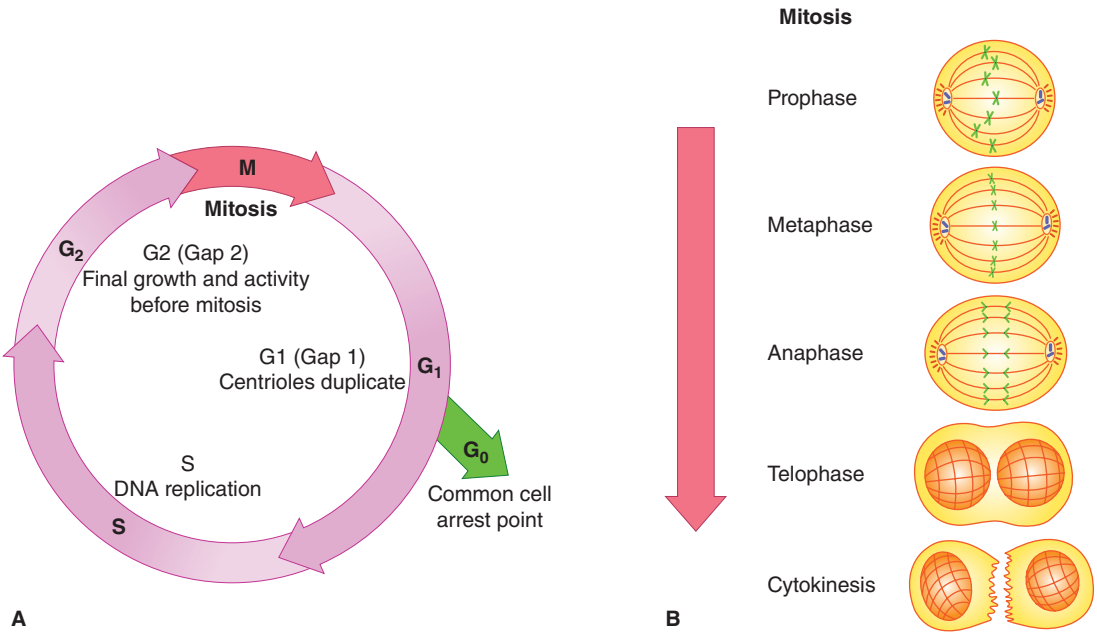


FIGURE 1–13 Sequence of events during the cell cycle. A) Immediately following mitosis (M) the cell enters a gap phase (G_1). At this point many cells will undergo cell arrest (G_0 phase). G_1 is followed by a DNA synthesis phase (S), a second gap phase (G_2) and back to mitosis. **B)** Stages of mitosis are highlighted.

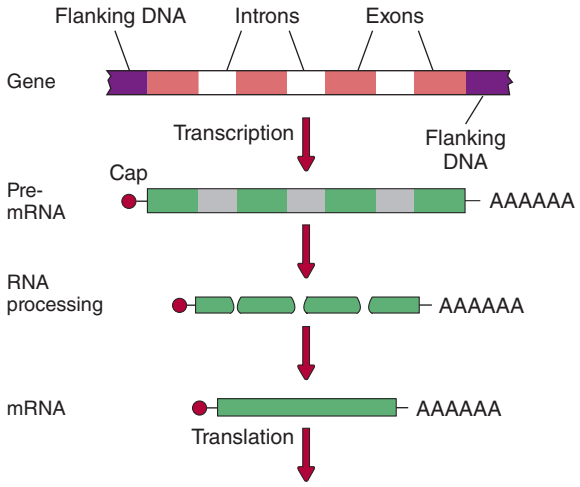


FIGURE 1–14 Transcription of a typical mRNA. Steps in transcription from a typical gene to a processed mRNA are shown. Cap, cap site; AAAAAA, poly(A) site.

are eliminated by **self-splicing** by the RNA they contain. Because of introns and splicing, more than one mRNA can be formed from the same gene.

Most forms of RNA in the cell are involved in **translation,** or protein synthesis. A brief outline of the transition from transcription to translation is shown in **Figure 1–15**. In the cytoplasm, ribosomes provide a template for tRNA to deliver specific amino acids to a growing polypeptide chain based on specific sequences in mRNA. The mRNA molecules are smaller than the DNA molecules, and each represents a transcript of a small segment of the DNA chain. For comparison, the molecules of tRNA contain only 70–80 nitrogenous bases, compared with hundreds in mRNA and 3 billion in DNA. A newer class of RNA, **microRNAs,** have recently been reported. MicroRNAs measure approximately 21–25 nucleotides in length and have been shown to negatively regulate gene expression at the posttranscriptional level. It is expected that

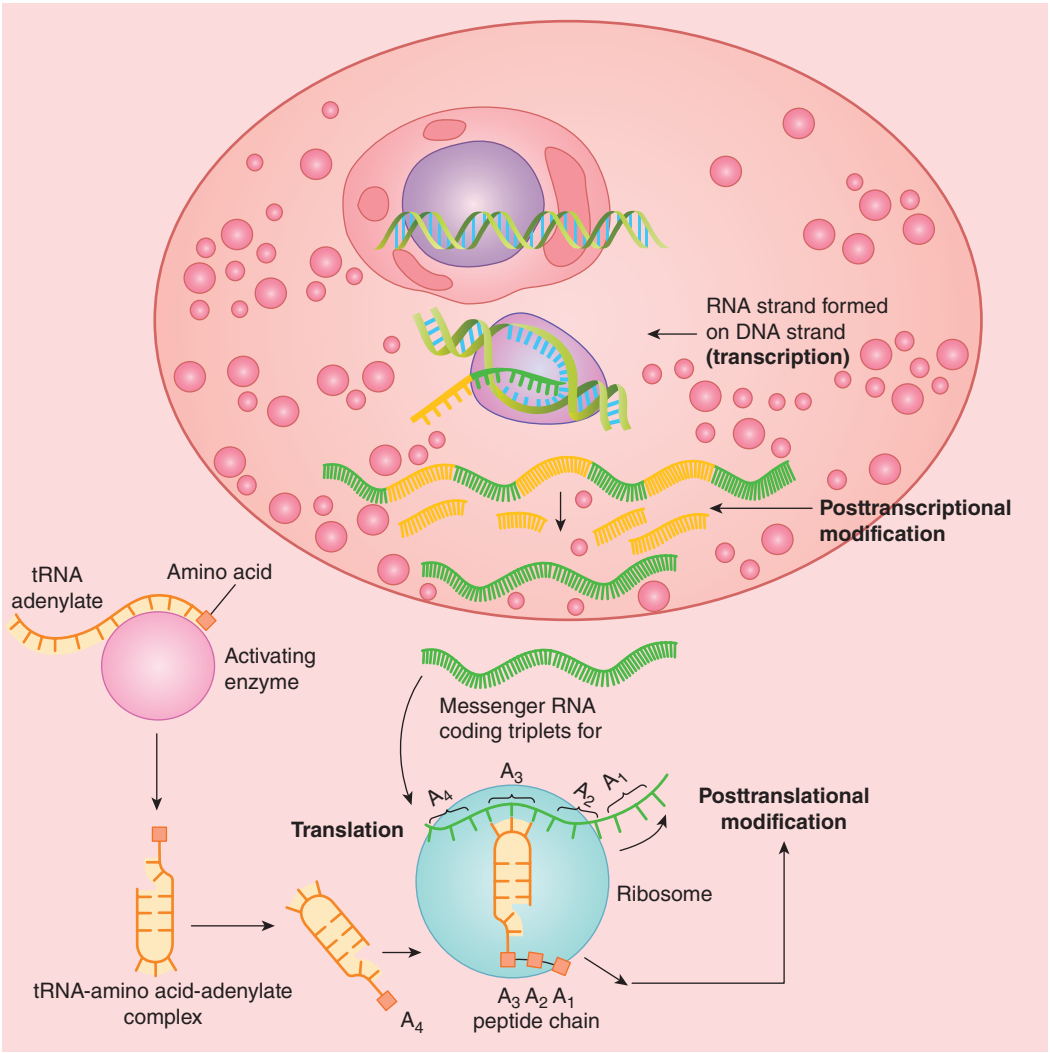


FIGURE 1–15 Diagrammatic outline of transcription to translation. In the nucleus, a messenger RNA is produced from the DNA molecule. This messenger RNA is processed and moved to the cytosol where it is presented to the ribosome. It is at the ribosome where charged tRNA match up with their complementary codons of mRNA to position the amino acid for growth of the polypeptide chain. The lines with multiple short projections in DNA and RNA represent individual bases. Small boxes labeled A represent individual amino acids.

roles for these small RNAs will continue to expand as research into their function continues.

AMINO ACIDS & PROTEINS

AMINO ACIDS

Amino acids that form the basic building blocks for proteins are identified in **Table 1–3.** These amino acids are often referred to by their corresponding three-letter, or single-letter abbreviations (eg, Ala or A for alanine). Various other important amino acids such as ornithine, 5-hydroxytryptophan, L-dopa, taurine, and thyroxine (T_4) are present in the body but are not found in proteins. In higher animals, the L isomers of the amino acids are the only naturally occurring forms in proteins. The L isomers of hormones such as thyroxine are much more active than the D isomers. The amino acids are acidic, neutral, or basic, depending on the relative proportions of free acidic (–COOH) or basic ($–NH_2$) groups in the molecule. Some of the amino acids are **nutritionally essential amino acids,** that is, they must be obtained in the diet, because they cannot be made in the body. Arginine and histidine must be provided through diet during times of rapid growth or recovery from illness and are termed **conditionally essential.** All others are **nonessential amino acids** in the sense that they can be synthesized in vivo in amounts sufficient to meet metabolic needs.

TABLE 1–3 Amino acids found in proteins.

Amino acids with aliphatic side chains	Amino acids with acidic side chains, or their amides
Glycine (Gly, G)	Aspartic acid (Asp, D)
Alanine (Ala, A)	Asparagine (Asn, N)
Valine (Val, V)	Glutamine (Gln, Q)
Leucine (Leu, L)	Glutamic acid (Glu, E)
Isoleucine (Ile, I)	γ-Carboxyglutamic acid[b] (Gla)
Hydroxyl-substituted amino acids	Amino acids with side chains containing basic groups
Serine (Ser, S)	***Arginine***[c] (Arg, R)
Threonine (Thr, T)	**Lysine** (Lys, K)
Sulfur-containing amino acids	Hydroxylysine[b] (Hyl)
Cysteine (Cys, C)	***Histidine***[c] (His, H)
Methionine (Met, M)	Imino acids (contain imino group but no amino group)
Selenocysteine[a]	Proline (Pro, P)
Amino acids with aromatic ring side chains	4-Hydroxyproline[b] (Hyp)
Phenylalanine (Phe, F)	3-Hydroxyproline[b]
Tyrosine (Tyr, Y)	
Tryptophan (Trp, W)	

Those in bold type are the nutritionally essential amino acids or conditionally essential amino acids. The generally accepted three-letter and one-letter abbreviations for the amino acids are shown in parentheses.

[a]Selenocysteine is a rare amino acid in which the sulfur of cysteine is replaced by selenium. The codon UGA is usually a stop codon, but in certain situations, it codes for selenocysteine.

[b]There are no tRNAs for these four amino acids; they are formed by posttranslational modification of the corresponding unmodified amino acid in peptide linkage. There are tRNAs for selenocysteine and the remaining 20 amino acids, and they are incorporated into peptides and proteins under direct genetic control.

[c]Arginine and histidine are sometimes called "conditionally essential"—they are not necessary for the maintenance of nitrogen balance, but are needed for normal growth (especially for children).

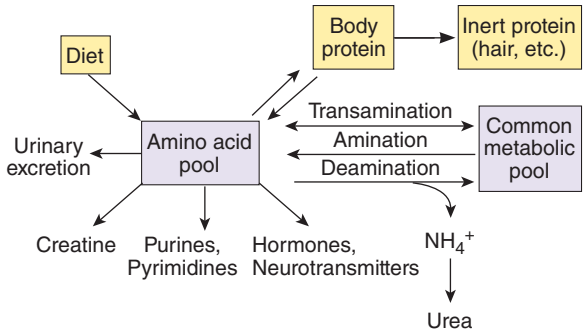


FIGURE 1–16 Amino acids in the body. There is an extensive network of amino acid turnover in the body. Boxes represent large pools of amino acids and some of the common interchanges are represented by arrows. Note that most amino acids come from the diet and end up in protein; however, a large portion of amino acids are interconverted and can feed into and out of a common metabolic pool through amination reactions.

THE AMINO ACID POOL

Although small amounts of proteins are absorbed from the gastrointestinal tract and some peptides are also absorbed, most ingested proteins are digested into their constituent amino acids before absorption. Traditionally, peptides are defined as molecules that consist of 2–100 amino acids, while proteins are made up of 100 or more amino acids. The body's proteins are being continuously hydrolyzed to amino acids and resynthesized. The turnover rate of endogenous proteins averages 80–100 g/day, being highest in the intestinal mucosa and practically nil in the extracellular structural protein, collagen. The amino acids formed by endogenous protein breakdown are identical to those derived from ingested protein. Together they form a common **amino acid pool** that supplies the needs of the body **(Figure 1–16)**.

PROTEINS

Proteins are made up of large numbers of amino acids linked into chains by **peptide bonds** joining the amino group of one amino acid to the carboxyl group of the next **(Figure 1–17)**. In addition, some proteins contain carbohydrates (glycoproteins) and lipids (lipoproteins). Smaller chains of amino acids are called **peptides** or **polypeptides.** The boundaries between peptides, polypeptides, and proteins are not well defined. For this text, amino acid chains containing 2–10 amino acid residues are called peptides, chains containing more than 10 but fewer than 100 amino acid residues are called polypeptides, and chains containing 100 or more amino acid residues are called proteins.

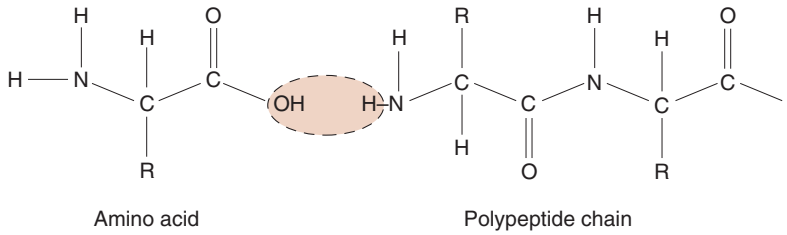


FIGURE 1–17 Amino acid structure and formation of peptide bonds. The dashed line shows where peptide bonds are formed between two amino acids. The highlighted area is released as H_2O. R, remainder of the amino acid. For example, in glycine, R = H; in glutamate, R = —$(CH_2)_2$—COO^-.

The order of the amino acids in the peptide chains is called the **primary structure** of a protein. The chains are twisted and folded in complex ways, and the term **secondary structure** of a protein refers to the spatial arrangement produced by the twisting and folding. A common secondary structure is a regular coil with 3.7 amino acid residues per turn (α-helix). Another common secondary structure is a β-sheet. An antiparallel β-sheet is formed when extended polypeptide chains fold back and forth on one another and hydrogen bonding occurs between the peptide bonds on neighboring chains. Parallel β-sheets between polypeptide chains also occur. The **tertiary structure** of a protein is the arrangement of the twisted chains into layers, crystals, or fibers. Many protein molecules are made of several proteins, or subunits (eg, hemoglobin), and the term **quaternary structure** is used to refer to the arrangement of the subunits into a functional structure.

PROTEIN SYNTHESIS

The process of protein synthesis, **translation,** is the conversion of information encoded in mRNA to a protein (Figure 1–15). As described previously, when a definitive mRNA reaches a ribosome in the cytoplasm, it dictates the formation of a polypeptide chain. Amino acids in the cytoplasm are activated by combination with an enzyme and AMP (adenylate), and each **activated amino acid** then combines with a specific molecule of tRNA. There is at least one tRNA for each of the 20 unmodified amino acids found in large quantities in the body proteins of animals, but some amino acids have more than one tRNA. The tRNA–amino acid–adenylate complex is next attached to the mRNA template, a process that occurs in the ribosomes. The tRNA "recognizes" the proper spot to attach on the mRNA template because it has on its active end a set of three bases that are complementary to a set of three bases in a particular spot on the mRNA chain. The genetic code is made up of such triplets **(codons),** sequences of three purine, pyrimidine, or purine and pyrimidine bases; each codon stands for a particular amino acid.

Translation typically starts in the ribosomes with an AUG (transcribed from ATG in the gene), which codes for methionine. The amino terminal (or N-terminal) amino acid is then added, and the chain is lengthened one amino acid at a time. The mRNA attaches to the 40S subunit of the ribosome during protein synthesis, the polypeptide chain being formed attaches to the 60S subunit, and the tRNA attaches to both. As the amino acids are added in the order dictated by the codon, the ribosome moves along the mRNA molecule like a bead on a string. Translation stops at one of three stops, or nonsense, codons (UGA, UAA, or UAG), and the polypeptide chain is released. The tRNA molecules are used again. The mRNA molecules are typically reused approximately 10 times before being replaced. It is common to have more than one ribosome on a given mRNA chain at a time. The mRNA chain plus its collection of ribosomes is visible under the electron microscope as an aggregation of ribosomes called a **polyribosome.**

POSTTRANSLATIONAL MODIFICATION

After the polypeptide chain is formed, it "folds" into its biological form and can be further modified to the final protein by one or more of a combination of reactions that include hydroxylation, carboxylation, glycosylation, or phosphorylation of amino acid residues; cleavage of peptide bonds that converts a larger polypeptide to a smaller form; and the further folding, packaging, or folding and packaging of the protein into its ultimate, often complex configuration. Protein folding is a complex process that is dictated primarily by the sequence of the amino acids in the polypeptide chain. In some instances, however, nascent proteins associate with other proteins called **chaperones,** which prevent inappropriate contacts with other proteins and ensure that the final "proper" conformation of the nascent protein is reached.

Proteins also contain information that helps direct them to individual cell compartments. Many proteins that are destined to be secreted or stored in organelles and most transmembrane proteins have at their amino terminal a **signal peptide (leader sequence)** that guides them into the endoplasmic reticulum. The sequence is made up of 15–30 predominantly hydrophobic amino acid residues. The signal peptide, once synthesized, binds to a **signal recognition particle (SRP),** a complex molecule made up of six polypeptides and 7S RNA, one of the small RNAs. The SRP stops translation until it binds to a **translocon,** a pore in the endoplasmic reticulum that is a heterotrimeric structure made up of Sec 61 proteins. The ribosome also binds, and the signal peptide leads the growing peptide chain into the cavity of the endoplasmic reticulum **(Figure 1–18)**.

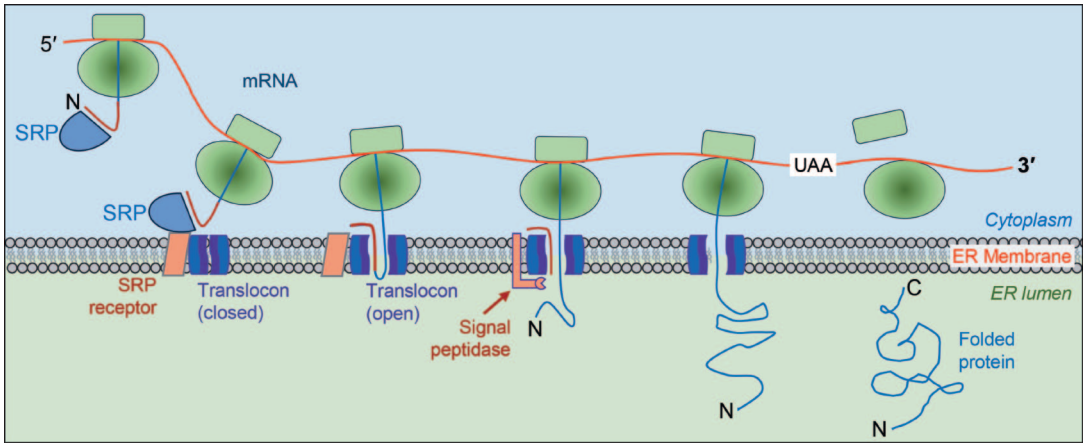


FIGURE 1–18 Translation of protein into the endoplasmic reticulum according to the signal hypothesis. The ribosomes synthesizing a protein move along the mRNA from the 5′ to the 3′ end. When the signal peptide of a protein destined for secretion, the cell membrane, or lysosomes, emerges from the large unit of the ribosome, it binds to a signal recognition particle (SRP), and this arrests further translation until it binds to the translocon on the endoplasmic reticulum. C, carboxyl end of protein; N, amino end of protein.

The signal peptide is next cleaved from the rest of the peptide by a signal peptidase while the rest of the peptide chain is still being synthesized. SRPs are not the only signals that help direct proteins to their proper place in or out of the cell; other signal sequences, posttranslational modifications, or both (eg, glycosylation) can serve this function.

UBIQUITINATION & PROTEIN DEGRADATION

Like protein synthesis, protein degradation is a carefully regulated, complex process. It has been estimated that overall, up to 30% of newly produced proteins are abnormal, such as can occur during improper folding. Aged normal proteins also need to be removed as they are replaced. Conjugation of proteins to the 74-amino-acid polypeptide **ubiquitin** marks them for degradation. This polypeptide is highly conserved and is present in species ranging from bacteria to humans. The process of binding ubiquitin is called **ubiquitination,** and in some instances, multiple ubiquitin molecules bind **(polyubiquitination).** Ubiquitination of cytoplasmic proteins, including integral proteins of the endoplasmic reticulum, can mark the proteins for degradation in multisubunit proteolytic particles, or **proteasomes.** Ubiquitination of membrane proteins, such as the growth hormone receptors, also marks them for degradation; however, these can be degraded in lysosomes as well as via the proteasomes. Alteration of proteins by ubiquitin or the small ubiquitin-related modifier **(SUMO),** however, does not necessarily lead to degradation. More recently it has been shown that these posttranslational modifications can play important roles in protein–protein interactions and various cellular signaling pathways.

There is an obvious balance between the rate of production of a protein and its destruction, so ubiquitin conjugation is of major importance in cellular physiology. The rates at which individual proteins are metabolized vary, and the body has mechanisms by which abnormal proteins are recognized and degraded more rapidly than normal body constituents. For example, abnormal hemoglobins are metabolized rapidly in individuals with congenital hemoglobinopathies (see Chapter 31).

CATABOLISM OF AMINO ACIDS

The short-chain fragments produced by amino acid, carbohydrate, and fat catabolism are very similar (see below). From this **common metabolic pool** (Figure 1–16) of intermediates, carbohydrates, proteins, and fats can be synthesized. These fragments can enter the citric acid cycle (or tricarboxylic acid cycle or Krebs cycle), a final common pathway of catabolism, in which they are broken down to hydrogen atoms and CO_2. Interconversion of amino acids involves transfer, removal, or formation of amino groups. **Transamination** reactions, conversion of one amino acid to the corresponding keto acid with simultaneous conversion of another keto acid to an amino acid, occur in many tissues:

$$\text{Alanine} + \alpha\text{–Ketoglutarate} \rightleftharpoons \text{Pyruvate} + \text{Glutamate}$$

Oxidative deamination of amino acids occurs in the liver. An imino acid is formed by dehydrogenation, and this compound is hydrolyzed to the corresponding keto acid, with production of NH_4^+:

$$\text{Amino acid} + NAD^+ \rightarrow \text{Imino acid} + NADH + H^+$$
$$\text{Imino acid} + H_2O \rightarrow \text{Keto acid} + NH_4^+$$

Interconversions between the amino acid pool and the common metabolic pool are summarized in **Figure 1–19.** Leucine, isoleucine, phenylalanine, and tyrosine are said to be **ketogenic** because they are converted to the ketone body acetoacetate (see following text). Alanine and many other amino acids

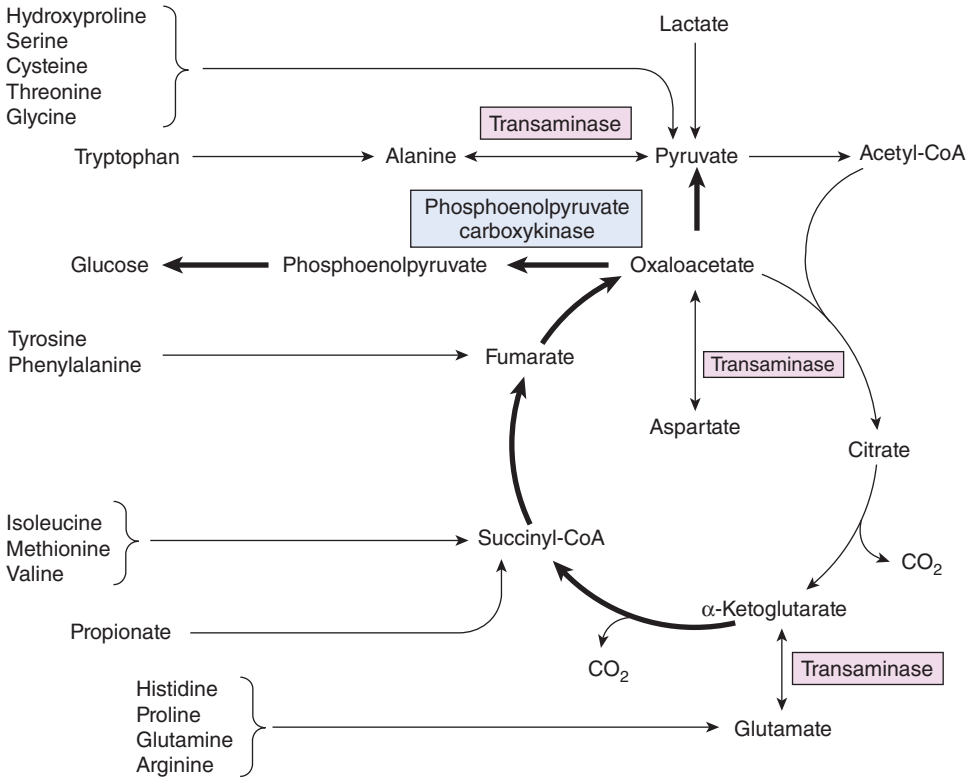


FIGURE 1–19 Involvement of the citric acid cycle in transamination and gluconeogenesis. The bold arrows indicate the main pathway of gluconeogenesis. Note the many entry positions for groups of amino acids into the citric acid cycle. (Reproduced with permission from Murray RK et al: *Harper's Biochemistry,* 28th ed. New York, NY: McGraw-Hill; 2009.)

are **glucogenic** or **gluconeogenic;** that is, they give rise to compounds that can readily be converted to glucose.

UREA FORMATION

Most of the NH_4^+ formed by deamination of amino acids in the liver is converted to urea, and the urea is excreted in the urine. The NH_4^+ forms carbamoyl phosphate, and in the mitochondria, it is transferred to ornithine, forming citrulline. The enzyme involved is ornithine carbamoyltransferase. Citrulline is converted to arginine, after which urea is split off and ornithine is regenerated (urea cycle; **Figure 1–20**). The overall reaction in the urea cycle consumes 3 ATP (not shown) and thus requires significant energy. Most of the urea is formed in the liver, and in severe liver disease, the blood urea nitrogen (BUN) falls and blood NH_3 rises (see Chapter 28). Congenital deficiency of ornithine carbamoyltransferase can also lead to NH_3 intoxication.

METABOLIC FUNCTIONS OF AMINO ACIDS

In addition to providing the basic building blocks for proteins, amino acids also have metabolic functions. Thyroid hormones, catecholamines, histamine, serotonin, melatonin, and intermediates in the urea cycle are formed from specific amino acids. Methionine and cysteine provide the sulfur contained in proteins, CoA, taurine, and other biologically important compounds. Methionine is converted into S-adenosyl methionine, which is the active methylating agent in the synthesis of compounds such as epinephrine.

CARBOHYDRATES

Carbohydrates are organic molecules made of equal amounts of carbon and H_2O. The simple sugars, or **monosaccharides,** including **pentoses** (five carbons; eg, ribose) and **hexoses** (six carbons; eg, glucose) perform both structural (eg, as part of nucleotides discussed previously) and functional (eg, inositol 1,4,5 trisphosphate acts as a cellular signaling molecule) roles in the body. Monosaccharides can be linked together to form disaccharides (eg, sucrose), or polysaccharides (eg, glycogen). The placement of sugar moieties onto proteins (glycoproteins) aids in cellular targeting, and in the case of some receptors, recognition of signaling molecules. In this section, the major role of carbohydrates in the production and storage of energy will be discussed.

Dietary carbohydrates are for the most part polymers of hexoses, of which the most important are glucose, galactose, and fructose. Most of the monosaccharides occurring in the body are the D isomers. The principal product of carbohydrate digestion and the principal circulating sugar is glucose. The normal

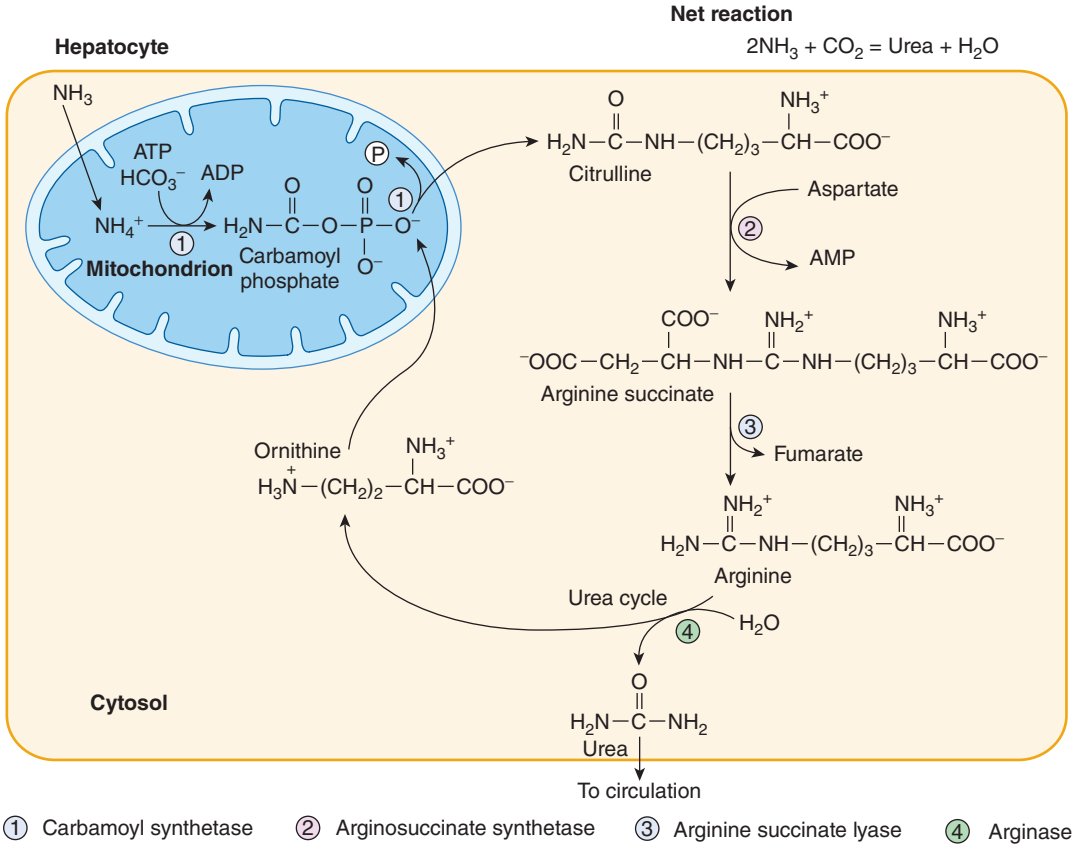


FIGURE 1–20 Urea cycle. The processing of NH_3 to urea for excretion contains coordinative steps in both the cytosol and the mitochondrion of a hepatocyte. Note that the production of carbamoyl phosphate and its conversion to citrulline occurs in the mitochondria, whereas other processes are in the cytoplasm.

fasting level of plasma glucose in peripheral venous blood is 70–110 mg/dL (3.9–6.1 mmol/L). In arterial blood, the plasma glucose level is 15–30 mg/dL higher than in venous blood.

Once it enters cells, glucose is normally phosphorylated to form glucose-6-phosphate. The enzyme that catalyzes this reaction is **hexokinase.** In the liver, there is an additional enzyme, **glucokinase,** which has greater specificity for glucose and which, unlike hexokinase, is increased by insulin and decreased in starvation and diabetes. The glucose-6-phosphate is either polymerized into glycogen or catabolized. The process of glycogen formation is called **glycogenesis,** and glycogen breakdown is called **glycogenolysis.** Glycogen, the storage form of glucose, is present in most body tissues, but the major supplies are in the liver and skeletal muscle. The breakdown of glucose to pyruvate or lactate (or both) is called **glycolysis.** Glucose catabolism proceeds via cleavage through fructose to trioses or via oxidation and decarboxylation to pentoses. The pathway to pyruvate through the trioses is the **Embden–Meyerhof pathway,** and that through 6-phosphogluconate and the pentoses is the **direct oxidative pathway (hexose monophosphate shunt).** Pyruvate is converted to acetyl-CoA. Interconversions between carbohydrate, fat, and protein include the conversion of the glycerol from fats to dihydroxyacetone phosphate and the conversion of a number of amino acids with carbon skeletons resembling intermediates in the Embden–Meyerhof pathway and citric acid cycle to these intermediates by deamination. In this way, and by conversion of lactate to glucose, nonglucose molecules can be converted to glucose **(gluconeogenesis).** Glucose can be converted to fats through acetyl-CoA, but because the conversion of pyruvate to acetyl-CoA, unlike most reactions in glycolysis, is irreversible, fats are not converted to glucose via this pathway. There is, therefore, very little net conversion of fats to carbohydrates in the body because, except for the quantitatively unimportant production from glycerol, there is no pathway for conversion.

CITRIC ACID CYCLE

The **citric acid cycle** (Krebs cycle, tricarboxylic acid cycle) produces ATP through a sequence of reactions in which acetyl-CoA is metabolized to CO_2 and H atoms. Acetyl-CoA is first condensed with the anion of a four-carbon acid, oxaloacetate, to form citrate and HS-CoA. In a series of seven subsequent reactions, 2 CO_2 molecules are split off, regenerating oxaloacetate **(Figure 1–21).** Four pairs of H atoms are transferred to the flavoprotein–cytochrome chain, producing 12 ATP and 4 H_2O, of which 2 H_2O are used in the cycle. The citric acid cycle is the common pathway for oxidation to CO_2 and H_2O of

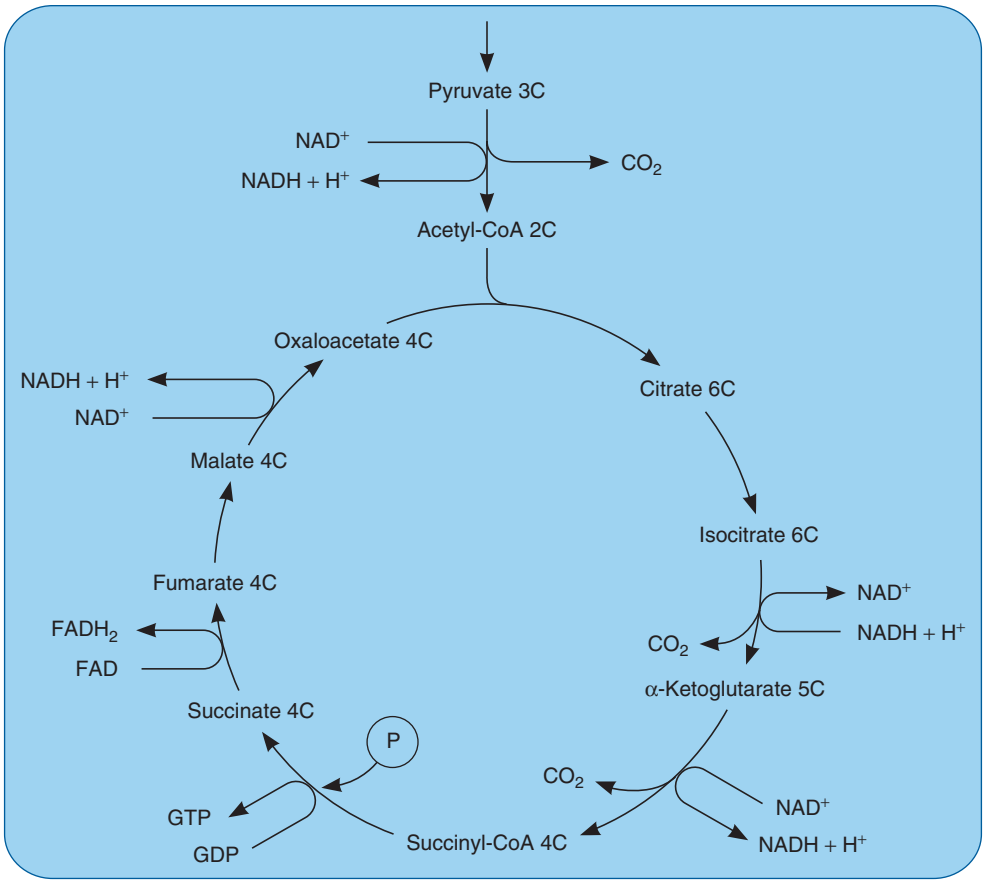


FIGURE 1–21 **Citric acid cycle.** The numbers (6C, 5C, etc.) indicate the number of carbon atoms in each of the intermediates. The conversion of pyruvate to acetyl-CoA and each turn of the cycle provides four NADH and one $FADH_2$ for oxidation via the flavoprotein-cytochrome chain plus formation of one GTP that is readily converted to ATP.

carbohydrate, fat, and some amino acids. The major entry into it is through acetyl CoA, but a number of amino acids can be converted to citric acid cycle intermediates by deamination. The citric acid cycle requires O_2 and does not function under anaerobic conditions.

ENERGY PRODUCTION

The net production of energy-rich phosphate compounds during the metabolism of glucose and glycogen to pyruvate depends on whether metabolism occurs via the Embden–Meyerhof pathway or the hexose monophosphate shunt. By oxidation at the substrate level, the conversion of 1 mol of phosphoglyceraldehyde to phosphoglycerate generates 1 mol of ATP, and the conversion of 1 mol of phosphoenolpyruvate to pyruvate generates another. Because 1 mol of glucose-6-phosphate produces, via the Embden–Meyerhof pathway, 2 mol of phosphoglyceraldehyde, 4 mol of ATP is generated per mole of glucose metabolized to pyruvate. All these reactions occur in the absence of O_2 and consequently represent anaerobic production of energy. However, 1 mol of ATP is used in forming fructose 1,6-diphosphate from fructose 6-phosphate and 1 mol in phosphorylating glucose when it enters the cell. Consequently, when pyruvate is formed anaerobically from glycogen, there is a *net* production of 3 mol of ATP per mole of glucose-6-phosphate; however, when pyruvate is formed from 1 mol of blood glucose, the net gain is only 2 mol of ATP.

A supply of NAD^+ is necessary for the conversion of phosphoglyceraldehyde to phosphoglycerate. Under anaerobic conditions (anaerobic glycolysis), a block of glycolysis at the phosphoglyceraldehyde conversion step might be expected to develop as soon as the available NAD^+ is converted to NADH. However, pyruvate can accept hydrogen from NADH, forming NAD^+ and lactate:

$$\text{Pyruvate} + \text{NADH} \rightleftharpoons \text{Lactate} + \text{NAD}^+$$

In this way, glucose metabolism and energy production can continue for a while without O_2. The lactate that accumulates is converted back to pyruvate when the O_2 supply is restored, with NADH transferring its hydrogen to the flavoprotein–cytochrome chain.

During aerobic glycolysis, the net production of ATP is 19 times greater than the 2 ATPs formed under anaerobic conditions. Six ATPs are formed by oxidation, via the flavoprotein–cytochrome chain, of the 2 NADHs produced when 2 molecules of phosphoglyceraldehyde are converted to

phosphoglycerate (Figure 1–21), 6 ATPs are formed from the 2 NADHs produced when 2 molecules of pyruvate are converted to acetyl-CoA, and 24 ATPs are formed during the subsequent two turns of the citric acid cycle. Of these, 18 are formed by oxidation of 6 NADHs, 4 by the oxidation of 2 $FADH_2$s, and 2 by oxidation at the substrate level, when succinyl-CoA is converted to succinate (this reaction actually produces guanosine triphosphate [GTP], but the GTP is converted to ATP). Thus, the net production of ATP per mol of blood glucose metabolized aerobically via the Embden–Meyerhof pathway and the citric acid cycle is 38 = 2 + [2 × 3] + [2 × 3] + [2 × 12].

Glucose oxidation via the hexose monophosphate shunt generates large amounts of NADPH. A supply of this reduced coenzyme is essential for many metabolic processes. The pentoses formed in the process are building blocks for nucleotides (see below). The amount of ATP generated depends on the amount of NADPH converted to NADH and then oxidized.

"DIRECTIONAL-FLOW VALVES" IN METABOLISM

Metabolism is regulated by a variety of hormones and other factors. To bring about any net change in a particular metabolic process, regulatory factors obviously must drive a chemical reaction in one direction. Most of the reactions in intermediary metabolism are freely reversible, but there are a number of "directional-flow valves," that is, reactions that proceed in one direction under the influence of one enzyme or transport mechanism and in the opposite direction under the influence of another. Five examples in the intermediary metabolism of carbohydrate are shown in **Figure 1–22**. The different pathways for fatty acid synthesis and catabolism (see below) are another example. Regulatory factors exert their influence on metabolism by acting directly or indirectly at these directional-flow valves.

GLYCOGEN SYNTHESIS & BREAKDOWN

Glycogen is a branched glucose polymer with two types of glycoside linkages: 1:4α and 1:6α **(Figure 1–23)**. It is synthesized on **glycogenin,** a protein primer, from glucose-1-phosphate via uridine diphosphoglucose (UDPG). The enzyme **glycogen synthase** catalyses the final synthetic step. The availability of glycogenin is one of the factors determining the amount of glycogen synthesized. The breakdown of glycogen in 1:4α linkage is catalyzed by phosphorylase, whereas another enzyme catalyzes the breakdown of glycogen in 1:6α linkage.

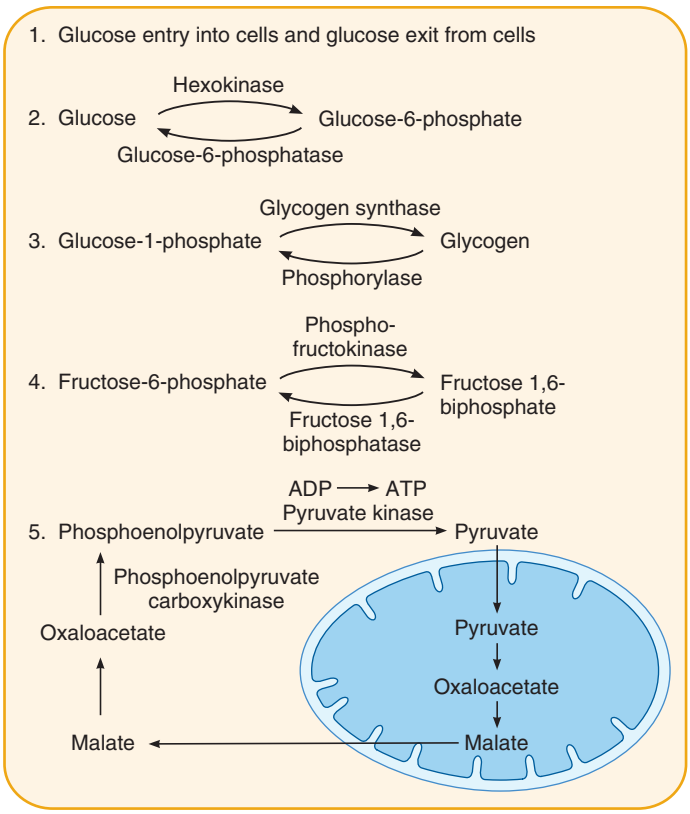


FIGURE 1–22 Directional-flow valves in energy production reactions. In carbohydrate metabolism there are several reactions that proceed in one direction by one mechanism and in the other direction by a different mechanism, termed "directional-flow valves." Five examples of these reactions are illustrated (numbered at left). The double line in example 5 represents the mitochondrial membrane. Pyruvate is converted to malate in mitochondria, and the malate diffuses out of the mitochondria to the cytosol, where it is converted to phosphoenolpyruvate.

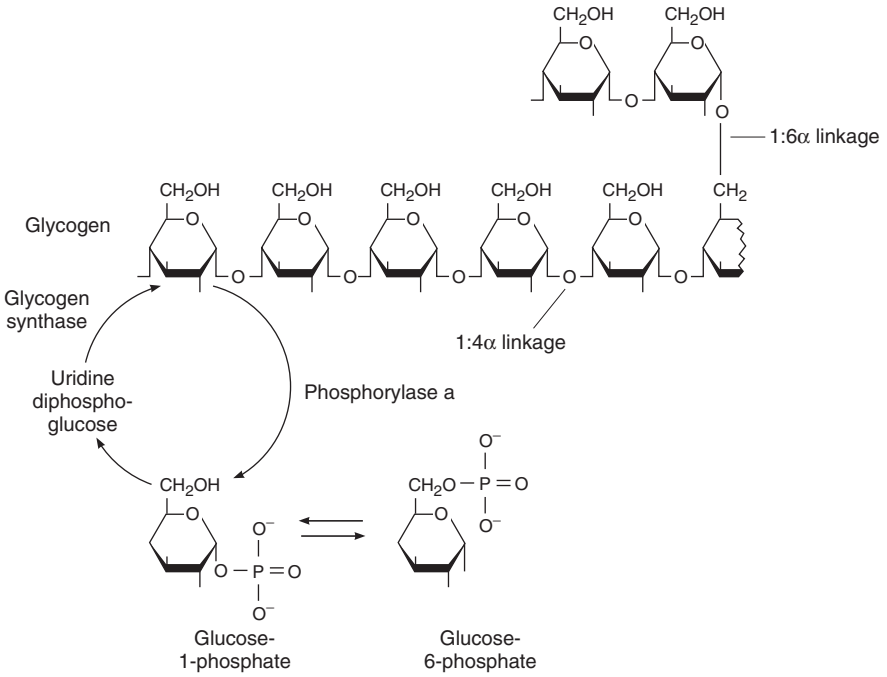


FIGURE 1–23 Glycogen synthesis and breakdown. Glycogen is the main storage for glucose in the cell. It is cycled: built up from glucose-6-phosphate when energy is stored and broken down to glucose-6-phosphate when energy is required. Note the intermediate glucose-1-phosphate and enzymatic control by phosphorylase and glycogen kinase.

FACTORS DETERMINING THE PLASMA GLUCOSE LEVEL

The blood plasma glucose level at any given time is determined by the balance between the amount of glucose entering the bloodstream and the amount of glucose leaving the bloodstream. The principal determinants are therefore the dietary intake; the rate of entry into the cells of muscle, adipose tissue, and other organs; and the glucostatic activity of the liver **(Figure 1–24)**. Five percent of ingested glucose is promptly converted into glycogen in the liver, and 30–40% is converted into fat. The remainder is metabolized in muscle and other tissues. During fasting, liver glycogen is broken down and the liver adds glucose to the bloodstream. With more prolonged fasting, glycogen is depleted and there is increased gluconeogenesis from amino acids and glycerol in the liver. Plasma glucose declines modestly to about 60 mg/dL during prolonged starvation in normal individuals, but symptoms of hypoglycemia do not occur because gluconeogenesis prevents any further fall.

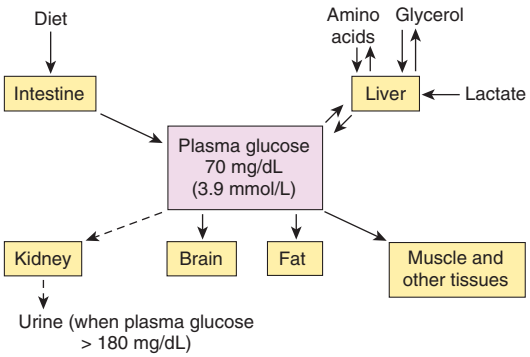


FIGURE 1–24 Plasma glucose homeostasis. Note the glucostatic function of the liver, as well as the loss of glucose in the urine when the renal threshold is exceeded (dashed arrows).

METABOLISM OF HEXOSES OTHER THAN GLUCOSE

Other hexoses that are absorbed from the intestine include galactose, which is liberated by the digestion of lactose and converted to glucose in the body; and fructose, part of which is ingested and part produced by hydrolysis of sucrose. After phosphorylation, galactose reacts with UDPG to form uridine diphosphogalactose. The uridine diphosphogalactose is converted back to UDPG, and the UDPG functions in glycogen synthesis. This reaction is reversible, and conversion of UDPG to uridine diphosphogalactose provides the galactose necessary for formation of glycolipids and mucoproteins when dietary galactose intake is inadequate. The utilization of galactose, like that of glucose, depends on insulin. The inability to make UDPG can have serious health consequences **(Clinical Box 1–5)**.

Fructose is converted in part to fructose 6-phosphate and then metabolized via fructose 1,6-diphosphate. The enzyme catalyzing the formation of fructose 6-phosphate is hexokinase, the same enzyme that catalyzes the conversion of glucose to glucose-6-phosphate. However, much more fructose is converted to

CLINICAL BOX 1–5

Galactosemia

In the inborn error of metabolism known as **galactosemia**, there is a congenital deficiency of galactose-1-phosphate uridyl transferase, the enzyme responsible for the reaction between galactose-1-phosphate and UDPG, so that ingested galactose accumulates in the circulation; serious disturbances of growth and development result.

THERAPEUTIC HIGHLIGHTS

Treatment with galactose-free diets improves galactosemia without leading to galactose deficiency. This occurs because the enzyme necessary for the formation of uridine diphosphogalactose from UDPG is present.

fructose 1-phosphate in a reaction catalyzed by fructokinase. Most of the fructose 1-phosphate is then split into dihydroxyacetone phosphate and glyceraldehyde. The glyceraldehyde is phosphorylated, and it and the dihydroxyacetone phosphate enter the pathways for glucose metabolism. Because the reactions proceeding through phosphorylation of fructose in the 1 position can occur at a normal rate in the absence of insulin, it has been recommended that fructose be given to diabetics to replenish their carbohydrate stores. However, most of the fructose is metabolized in the intestines and liver, so its value in replenishing carbohydrate elsewhere in the body is limited.

Fructose 6-phosphate can also be phosphorylated in the 2 position, forming fructose 2,6-diphosphate. This compound is an important regulator of hepatic gluconeogenesis. When the fructose 2,6-diphosphate level is high, conversion of fructose 6-phosphate to fructose 1,6-diphosphate is facilitated, and thus breakdown of glucose to pyruvate is increased. A decreased level of fructose 2,6-diphosphate facilitates the reverse reaction and consequently aids gluconeogenesis.

FATTY ACIDS & LIPIDS

The biologically important lipids are the fatty acids and their derivatives, the neutral fats (triglycerides), the phospholipids and related compounds, and the sterols. The triglycerides are made up of three fatty acids bound to glycerol **(Table 1–4).** Naturally occurring fatty acids contain an even number of carbon atoms. They may be saturated (no double bonds) or unsaturated (dehydrogenated, with various numbers of double bonds). The phospholipids are constituents of cell membranes and provide structural components of the cell membrane, as well as an important source of intracellular and intercellular signaling molecules. Fatty acids also are an important source of energy in the body.

TABLE 1–4 Lipids.

Typical fatty acids:

Palmitic acid: $CH_3(CH_2)_{14}—C(=O)—OH$

Stearic acid: $CH_3(CH_2)_{16}—C(=O)—OH$

Oleic acid: $CH_3(CH_2)_7CH{=}CH(CH_2)_7—C(=O)—OH$ (Unsaturated)

Triglycerides (triacylglycerols): Esters of glycerol and three fatty acids.

$$\begin{array}{l} CH_2—O—C(=O)—R \\ | \\ CH_2—O—C(=O)—R \\ | \\ CH_2—O—C(=O)—R \\ \text{Triglyceride} \end{array} + 3H_2O \rightleftarrows \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \\ \text{Glycerol} \end{array} + 3HO—C(=O)—R$$

R = Aliphatic chain of various lengths and degrees of saturation.

Phospholipids:

A. Esters of glycerol, two fatty acids, and
   1. Phosphate = phosphatidic acid
   2. Phosphate plus inositol = phosphatidylinositol
   3. Phosphate plus choline = phosphatidylcholine (lecithin)
   4. Phosphate plus ethanolamine = phosphatidyl-ethanolamine (cephalin)
   5. Phosphate plus serine = phosphatidylserine

B. Other phosphate-containing derivatives of glycerol.

C. Sphingomyelins: Esters of fatty acid, phosphate, choline, and the amino alcohol sphingosine.

Cerebrosides: Compounds containing galactose, fatty acid, and sphingosine.

Sterols: Cholesterol and its derivatives, including steroid hormones, bile acids, and various vitamins.

FATTY ACID OXIDATION & SYNTHESIS

In the body, fatty acids are broken down to acetyl-CoA, which enters the citric acid cycle. The main breakdown occurs in the mitochondria by β-oxidation. Fatty acid oxidation begins with activation (formation of the CoA derivative) of the fatty acid, a reaction that occurs both inside and outside the mitochondria. Medium- and short-chain fatty acids can enter the mitochondria without difficulty, but long-chain fatty acids must be bound to **carnitine** in ester linkage before they can cross the inner mitochondrial membrane. Carnitine is β-hydroxy-γ-trimethylammonium butyrate, and it is synthesized in the body from lysine and methionine. A translocase moves the fatty acid-carnitine ester into the matrix space. The ester is

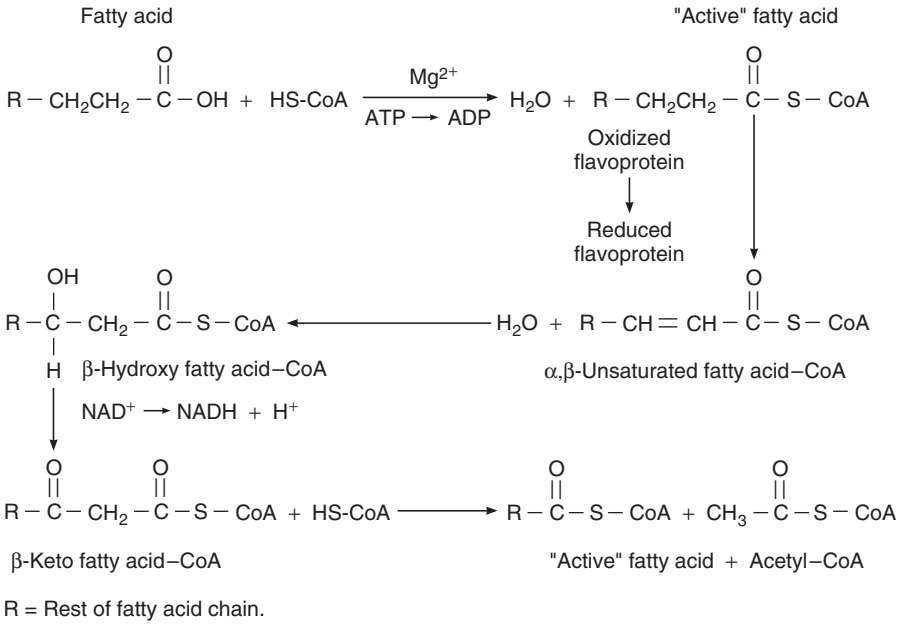


FIGURE 1–25 **Fatty acid oxidation.** This process, splitting off two carbon fragments at a time, is repeated to the end of the chain.

hydrolyzed, and the carnitine recycles. β-Oxidation proceeds by serial removal of two carbon fragments from the fatty acid **(Figure 1–25)**. The energy yield of this process is large. For example, catabolism of 1 mol of a six-carbon fatty acid through the citric acid cycle to CO_2 and H_2O generates 44 mol of ATP, compared with the 38 mol generated by catabolism of 1 mol of the six-carbon carbohydrate glucose.

KETONE BODIES

In many tissues, acetyl-CoA units condense to form acetoacetyl-CoA **(Figure 1–26)**. In the liver, which (unlike other tissues) contains a deacylase, free acetoacetate is formed. This β-keto acid is converted to β-hydroxybutyrate and acetone, and because these compounds are metabolized with difficulty in the liver, they diffuse into the circulation. Acetoacetate is also formed in the liver via the formation of 3-hydroxy-3-methylglutaryl-CoA, and this pathway is quantitatively more important than deacylation. Acetoacetate, β-hydroxybutyrate, and acetone are called **ketone bodies.** Tissues other than liver transfer CoA from succinyl-CoA to acetoacetate and metabolize the "active" acetoacetate to CO_2 and H_2O via the citric acid cycle. Ketone bodies are also metabolized via other pathways. Acetone is discharged in the urine and expired air. An imbalance of ketone bodies can lead to serious health problems **(Clinical Box 1–6)**.

CELLULAR LIPIDS

The lipids in cells are of two main types: **structural lipids,** which are an inherent part of the membranes and can serve as progenitors for cellular signaling molecules; and **neutral fat,** stored in the adipose cells of the fat depots. Neutral fat is mobilized during starvation, but structural lipid is preserved. The fat depots obviously vary in size, but in nonobese individuals they make up about 15% of body weight in men and 21% in women. They are not the inert structures they were once thought to be but, rather, active dynamic tissues undergoing continuous breakdown and resynthesis. In the depots, glucose is metabolized to fatty acids, and neutral fats are synthesized. Neutral fat is also broken down, and free fatty acids (FFAs) are released into the circulation.

A third, special type of lipid is **brown fat,** which makes up a small percentage of total body fat. Brown fat, which is somewhat more abundant in infants but is present in adults as well, is located between the scapulas, at the nape of the neck, along the great vessels in the thorax and abdomen, and in other scattered locations in the body. In brown fat depots, the fat cells as well as the blood vessels have an extensive sympathetic innervation. This is in contrast to white fat depots, in which some fat cells may be innervated but the principal sympathetic innervation is solely on blood vessels. In addition, ordinary lipocytes have only a single large droplet of white fat, whereas brown fat cells contain several small droplets of fat. Brown fat cells also contain many mitochondria. In these mitochondria, an inward proton conductance that generates ATP takes place as usual, but in addition there is a second proton conductance that does not generate ATP. This "short-circuit" conductance depends on a 32-kDa uncoupling protein (UCP1). It causes uncoupling of metabolism and generation of ATP, so that more heat is produced.

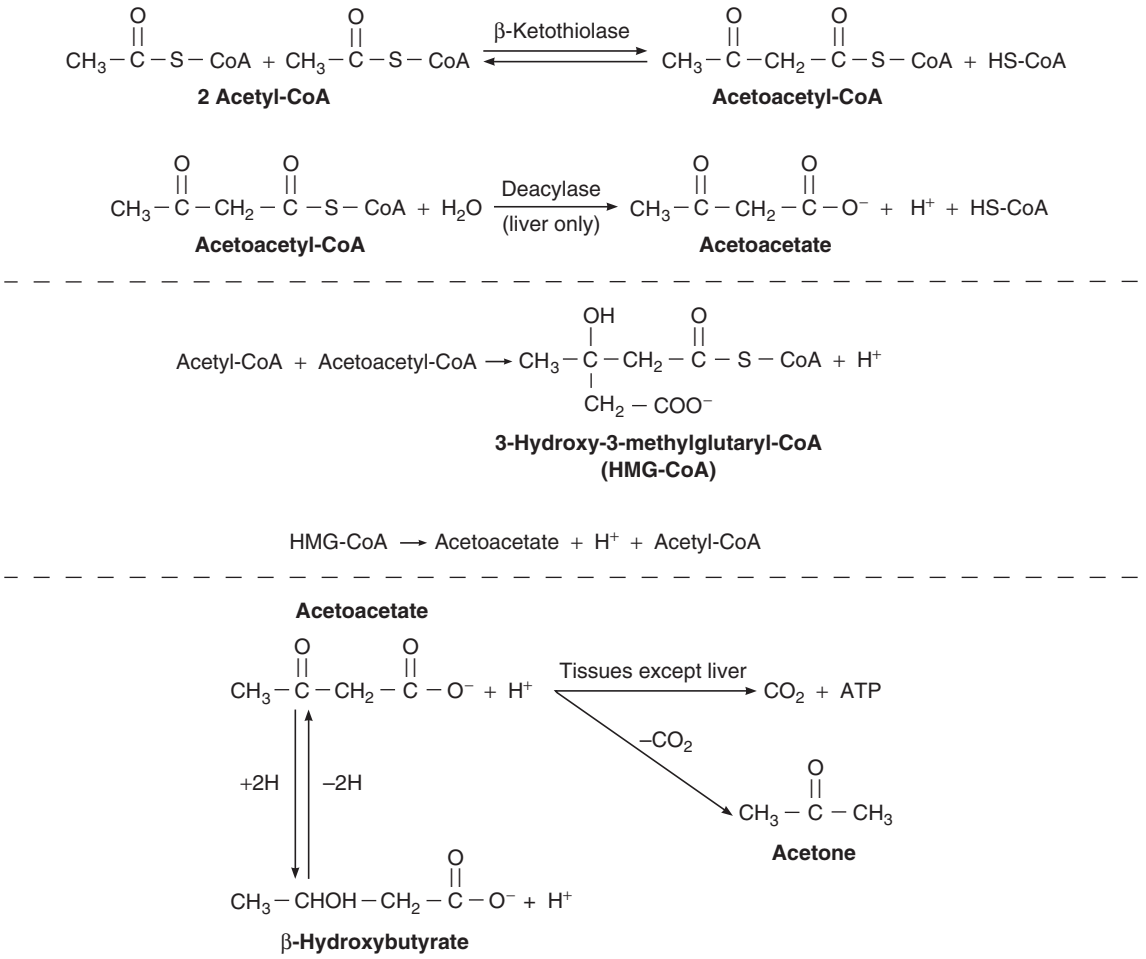


FIGURE 1–26 **Formation and metabolism of ketone bodies.** Note the two pathways for the formation of acetoacetate.

PLASMA LIPIDS & LIPID TRANSPORT

The major lipids are relatively insoluble in aqueous solutions and do not circulate in the free form. **FFAs** are bound to albumin, whereas cholesterol, triglycerides, and phospholipids are transported in the form of **lipoprotein** complexes. The complexes greatly increase the solubility of the lipids. The six families of lipoproteins **(Table 1–5)** are graded in size and lipid content. The density of these lipoproteins is inversely proportionate to their lipid content. In general, the lipoproteins consist of a hydrophobic core of triglycerides and cholesteryl esters surrounded by phospholipids and protein. These lipoproteins can be transported from the intestine to the liver via an **exogenous pathway,** and between other tissues via an **endogenous pathway.**

Dietary lipids are processed by several pancreatic lipases in the intestine to form mixed micelles of predominantly FFA, **2-monoacylglycerols,** and cholesterol derivatives (see Chapter 26). These micelles additionally can contain important water-insoluble molecules such as **vitamins A, D, E,** and **K.** These mixed micelles are taken up into cells of the intestinal mucosa where large lipoprotein complexes, **chylomicrons,** are formed. The chylomicrons and their remnants constitute a transport system for ingested exogenous lipids (exogenous pathway). Chylomicrons can enter the circulation via the lymphatic ducts. The chylomicrons are cleared from the circulation by the action of **lipoprotein lipase,** which is located on the surface of the endothelium of the capillaries. The enzyme catalyzes the breakdown of the triglyceride in the chylomicrons to FFA and glycerol, which then enter adipose cells and are reesterified. Alternatively, the FFA can remain in the circulation bound to albumin. Lipoprotein lipase, which requires heparin as a cofactor, also removes triglycerides from circulating **very low-density lipoproteins (VLDL).** Chylomicrons depleted of their triglyceride remain in the circulation as cholesterol-rich lipoproteins called **chylomicron remnants,** which are 30–80 nm in diameter. The remnants are carried to the liver, where they are internalized and degraded.

The endogenous system, made up of VLDL, **intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL),** and **high-density lipoproteins (HDL),** also transports triglycerides and cholesterol throughout the body. VLDL are formed in the liver and transport triglycerides formed

CLINICAL BOX 1–6

Diseases Associated with Imbalance of β-Oxidation of Fatty Acids

Ketoacidosis

The normal blood ketone level in humans is low (about 1 mg/dL) and less than 1 mg is excreted per 24 h, because the ketones are normally metabolized as rapidly as they are formed. However, if the entry of acetyl-CoA into the citric acid cycle is depressed because of a decreased supply of the products of glucose metabolism, or if the entry does not increase when the supply of acetyl-CoA increases, acetyl-CoA accumulates, the rate of condensation to acetoacetyl-CoA increases, and more acetoacetate is formed in the liver. The ability of the tissues to oxidize the ketones is soon exceeded, and they accumulate in the bloodstream (ketosis). Two of the three ketone bodies, acetoacetate and β-hydroxybutyrate, are anions of the moderately strong acids, acetoacetic acid and β-hydroxybutyric acid. Many of their protons are buffered, reducing the decline in pH that would otherwise occur. However, the buffering capacity can be exceeded, and the metabolic acidosis that develops in conditions such as diabetic ketosis can be severe and even fatal. Three conditions lead to deficient intracellular glucose supplies, and hence to ketoacidosis: starvation; diabetes mellitus; and a high-fat, low-carbohydrate diet. The acetone odor on the breath of children who have been vomiting is due to the ketosis of starvation. Parenteral administration of relatively small amounts of glucose abolishes the ketosis, and it is for this reason that carbohydrate is said to be antiketogenic.

Carnitine Deficiency

Deficient β-oxidation of fatty acids can be produced by carnitine deficiency or genetic defects in the translocase or other enzymes involved in the transfer of long-chain fatty acids into the mitochondria. This causes cardiomyopathy. In addition, it causes **hypoketonemic hypoglycemia** with coma, a serious and often fatal condition triggered by fasting, in which glucose stores are used up because of the lack of fatty acid oxidation to provide energy. Ketone bodies are not formed in normal amounts because of the lack of adequate CoA in the liver.

THERAPEUTIC HIGHLIGHTS

The primary treatment for diabetic ketoacidosis is to replace the lost fluids and electrolytes, while insulin is generally given to reverse the processes that cause diabetic ketoacidosis. The main treatment for primary carnitine deficiency is lifelong use of L-carnitine, a natural substance that helps body cells make energy and get rid of harmful wastes. L-carnitine can also reverse the heart problems and muscle weakness caused by carnitine deficiency. Pediatric patients with carnitine deficiency also benefit from a low-fat, high carbohydrate diet and drinking more fluids.

from fatty acids and carbohydrates in the liver to extrahepatic tissues. After their triglyceride is largely removed by the action of lipoprotein lipase, they become IDL. The IDL give up phospholipids and, through the action of the plasma enzyme **lecithin-cholesterol acyltransferase (LCAT),** pick up cholesteryl esters formed from cholesterol in the HDL. Some IDL are taken up by the liver. The remaining IDL then lose more triglyceride and protein, probably in the sinusoids of the liver, and become LDL. LDL provide cholesterol to the tissues. The cholesterol is an essential constituent in cell membranes and is used by gland cells to make steroid hormones.

FREE FATTY ACID METABOLISM

In addition to the exogenous and endogenous pathways described above, FFAs are also synthesized in the fat depots in which they are stored. They can circulate as lipoproteins bound to albumin and are a major source of energy for many organs. They are used extensively in the heart, but probably all tissues can oxidize FFA to CO_2 and H_2O.

The supply of FFA to the tissues is regulated by two lipases. As noted above, lipoprotein lipase on the surface of the endothelium of the capillaries hydrolyzes the triglycerides in chylomicrons and VLDL, providing FFA and glycerol, which are reassembled into new triglycerides in the fat cells. The intracellular **hormone-sensitive lipase** of adipose tissue catalyzes the breakdown of stored triglycerides into glycerol and fatty acids, with the latter entering the circulation. Hormone-sensitive lipase is increased by fasting and stress and decreased by feeding and insulin. Conversely, feeding increases and fasting and stress decrease the activity of lipoprotein lipase.

CHOLESTEROL METABOLISM

Cholesterol is the precursor of the steroid hormones and bile acids and is an essential constituent of cell membranes. It is found only in animals. Related sterols occur in plants, but plant sterols are poorly absorbed from the gastrointestinal tract. Most of the dietary cholesterol is contained in egg yolks and animal fat.

Cholesterol is absorbed from the intestine and incorporated into the chylomicrons formed in the intestinal mucosa. After the chylomicrons discharge their triglyceride in adipose

TABLE 1–5 The principal lipoproteins.[a]

Lipoprotein	Composition (%)						Origin
	Size (nm)	Protein	Free Cholesteryl	Cholesterol Esters	Triglyceride	Phospholipid	
Chylomicrons	75–1000	2	2	3	90	3	Intestine
Chylomicron remnants	30–80	…	…	…	…	…	Capillaries
Very low-density lipoproteins (VLDL)	30–80	8	4	16	55	17	Liver and intestine
Intermediate-density lipoproteins (IDL)	25–40	10	5	25	40	20	VLDL
Low-density lipoproteins (LDL)	20	20	7	46	6	21	IDL
High-density lipoproteins (HDL)	7.5–10	50	4	16	5	25	Liver and intestine

[a]The plasma lipids include these components plus free fatty acids from adipose tissue, which circulate bound to albumin.

tissue, the chylomicron remnants bring cholesterol to the liver. The liver and other tissues also synthesize cholesterol. Some of the cholesterol in the liver is excreted in the bile, both in the free form and as bile acids. Some of the biliary cholesterol is reabsorbed from the intestine. Most of the cholesterol in the liver is incorporated into VLDL and circulates in lipoprotein complexes.

The biosynthesis of cholesterol from acetate is summarized in Figure 1–27. Cholesterol feeds back to inhibit its own synthesis by inhibiting **HMG-CoA reductase,** the enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonic acid. Thus, when dietary cholesterol intake is high, hepatic cholesterol synthesis is decreased, and vice versa. However, the feedback compensation is incomplete, because a diet that is low in cholesterol and saturated fat leads to only a modest decline in circulating plasma cholesterol. The most effective and most commonly used cholesterol-lowering drugs are lovastatin and other **statins,** which reduce cholesterol synthesis by inhibiting HMG-CoA. The relationship between cholesterol and vascular disease is discussed in Clinical Box 1–7.

ESSENTIAL FATTY ACIDS

Animals fed a fat-free diet fail to grow, develop skin and kidney lesions, and become infertile. Adding linolenic, linoleic, and arachidonic acids to the diet cures all the deficiency symptoms. These three acids are polyunsaturated fatty acids and because of their action are called **essential fatty acids.** Similar deficiency symptoms have not been unequivocally demonstrated in humans, but there is reason to believe that some unsaturated fats are essential dietary constituents, especially for children. Dehydrogenation of fats is known to occur in the body, but there does not appear to be any synthesis of carbon chains with the arrangement of double bonds found in the essential fatty acids.

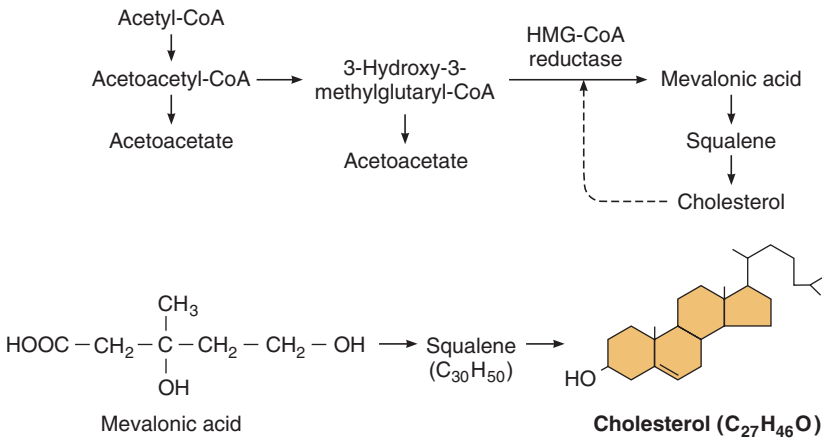


FIGURE 1–27 Biosynthesis of cholesterol. Six mevalonic acid molecules condense to form squalene, which is then hydroxylated to cholesterol. The dashed arrow indicates feedback inhibition by cholesterol of HMG-CoA reductase, the enzyme that catalyzes mevalonic acid formation.

CLINICAL BOX 1–7

Cholesterol & Atherosclerosis

The interest in cholesterol-lowering drugs stems from the role of cholesterol in the development and progression of **atherosclerosis**. This extremely widespread disease predisposes to myocardial infarction, cerebral thrombosis, ischemic gangrene of the extremities, and other serious illnesses. It is characterized by infiltration of cholesterol and oxidized cholesterol into macrophages, converting them into foam cells in lesions of the arterial walls. This is followed by a complex sequence of changes involving platelets, macrophages, and smooth muscle cells, as well as growth factors and inflammatory mediators that produces proliferative lesions that eventually ulcerate and may calcify. The lesions distort the vessels and make them rigid. In individuals with elevated plasma cholesterol levels, the incidence of atherosclerosis and its complications is increased. The normal range for plasma cholesterol is said to be 120–200 mg/dL, but in men, there is a clear, tight, positive correlation between the death rate from ischemic heart disease and plasma cholesterol levels above 180 mg/dL. Furthermore, it is now clear that lowering plasma cholesterol by diet and drugs slows and may even reverse the progression of atherosclerotic lesions and the complications they cause.

In evaluating plasma cholesterol levels in relation to atherosclerosis, it is important to analyze the LDL and HDL levels as well. LDL delivers cholesterol to peripheral tissues, including atheromatous lesions, and the LDL plasma concentration correlates positively with myocardial infarctions and ischemic strokes. On the other hand, HDL picks up cholesterol from peripheral tissues and transports it to the liver, thus lowering plasma cholesterol. It is interesting that women, who have a lower incidence of myocardial infarction than men, have higher HDL levels. In addition, HDL levels are increased in individuals who exercise and those who drink one or two alcoholic drinks per day, whereas they are decreased in individuals who smoke, are obese, or live sedentary lives. Moderate drinking decreases the incidence of myocardial infarction, and obesity and smoking are risk factors that increase it. Plasma cholesterol and the incidence of cardiovascular diseases are increased in **familial hypercholesterolemia,** due to various loss-of-function mutations in the genes for LDL receptors.

THERAPEUTIC HIGHLIGHTS

Although atherosclerosis is a progressive disease, it is also preventable in many cases by limiting risk factors, including lowering "bad" cholesterol through a healthy diet and exercise. Drug treatments for high cholesterol, including the statins among others, provide additional relief that can complement a healthy diet and exercise. If atherosclerosis is advanced, invasive techniques, such as angioplasty and stenting, can be used to unblock arteries.

EICOSANOIDS

One of the reasons that essential fatty acids are necessary for health is that they are the precursors of prostaglandins (including prostacyclin, thromboxanes), lipoxins, leukotrienes, and related compounds. These substances are called **eicosanoids,** reflecting their origin from the 20-carbon (eicosa-) polyunsaturated fatty acid **arachidonic acid (arachidonate)** and the 20-carbon derivatives of linoleic and linolenic acids.

The **prostaglandins** are a series of 20-carbon unsaturated fatty acids containing a cyclopentane ring. They were first isolated from semen but are synthesized in most and possibly in all organs in the body. Prostaglandin H_2 (PGH_2) is the precursor for various other prostaglandins, thromboxanes, and prostacyclin. Arachidonic acid is formed from tissue phospholipids by **phospholipase A2.** It is converted to prostaglandin H_2 (PGH_2) by **prostaglandin G/H synthases** 1 and 2. These are bifunctional enzymes that have both cyclooxygenase and peroxidase activities, but they are more commonly known by the names cyclooxygenase 1 **(COX1)** and cyclooxygenase 2 **(COX2).** Their structures are very similar, but COX1 is constitutive whereas COX2 is induced by growth factors, cytokines, and tumor promoters. PGH_2 is converted to prostacyclin, thromboxanes, and other prostaglandins (eg, PGE_2, $PGF_{2\alpha}$, PGD_2) by various tissue isomerases. The effects of prostaglandins are multitudinous and varied. They are particularly important in the female reproductive cycle, in parturition, in the cardiovascular system, in inflammatory responses, and in the causation of pain. Drugs that target production of prostaglandins are among the most common over-the-counter drugs available **(Clinical Box 1–8).**

Arachidonic acid also serves as a substrate for the production of several physiologically important **leukotrienes** and **lipoxins.** The leukotrienes, thromboxanes, lipoxins, and prostaglandins have been called local hormones. They have short half-lives and are inactivated in many different tissues. They undoubtedly act mainly in the tissues at sites in which they are produced. The leukotrienes are mediators of allergic responses and inflammation. Their release is provoked when specific allergens combine with IgE antibodies on the surfaces of mast cells (see Chapter 3). They produce bronchoconstriction, constrict arterioles, increase vascular permeability, and attract neutrophils and eosinophils to inflammatory sites. Diseases in which they may be involved include asthma, psoriasis, acute respiratory distress syndrome, allergic rhinitis, rheumatoid arthritis, Crohn disease, and ulcerative colitis.

CLINICAL BOX 1–8

Pharmacology of Prostaglandins

Because prostaglandins play a prominent role in the genesis of pain, inflammation, and fever, pharmacologists have long sought drugs to inhibit their synthesis. Glucocorticoids inhibit phospholipase A_2 and thus inhibit the formation of all eicosanoids. A variety of NSAIDs inhibit both cyclooxygenases, inhibiting the production of PGH_2 and its derivatives. Aspirin is the best-known of these, but ibuprofen, indomethacin, and others are also used. However, there is evidence that prostaglandins synthesized by COX2 are more involved in the production of pain and inflammation, and prostaglandins synthesized by COX1 are more involved in protecting the gastrointestinal mucosa from ulceration. Several novel NSAIDs have been introduced in an attempt to specifically target COX enzymes. However, in many cases, significant side effects, including increased incidence of stroke and heart attack, have led to drug withdrawals from the market. More research is underway to better understand all the effects of the COX enzymes, their products, and their inhibitors. Some prostaglandins can, however, be used as drugs for cardiovascular disease based on their vasodilative and antiproliferative effects. For example, intravenous perfusion of prostacyclin is an effective treatment for idiopathic pulmonary arterial hypertension, a progressive and fatal disease that predominantly affects young women.

CHAPTER SUMMARY

- Cells contain approximately two-thirds of the body fluids, while the remaining extracellular fluid is found between cells (interstitial fluid) or in the circulating lymph and blood plasma.
- The number of molecules, electrical charges, and particles of substances in solution are important in physiology.
- Biological buffers including bicarbonate, proteins, and phosphates can bind or release protons in solution to help maintain pH. Biological buffering capacity of a weak acid or base is greatest when pK_a = pH.
- Although the osmolality of solutions can be similar across a plasma membrane, the distribution of individual molecules and the distribution of charge across the plasma membrane can be quite different. The separation of concentrations of charged species sets up an electrical gradient at the plasma membrane (inside negative). The electrochemical gradient is in large part maintained by the Na, K ATPase. These are affected by the Gibbs–Donnan equilibrium and can be calculated using the Nernst equation.
- Cellular energy can be stored in high-energy or energy-rich phosphate compounds, including adenosine triphosphate (ATP). Coordinated oxidation-reduction reactions allow for the production of a proton gradient at the inner mitochondrial membrane that ultimately yields to the production of ATP in the cell.
- Nucleotides made from purine or pyrimidine bases linked to ribose or 2-deoxyribose sugars with inorganic phosphates are the basic building blocks for nucleic acids, DNA, and RNA. The fundamental unit of DNA is the gene, which encodes information to make proteins in the cell. Genes are transcribed into messenger RNA, and with the help of ribosomal RNA and transfer RNAs, translated into proteins.
- Amino acids are the basic building blocks for proteins in the cell and can also serve as sources for several biologically active molecules. Translation is the process of protein synthesis. After synthesis, proteins can undergo a variety of posttranslational modifications prior to obtaining their full function in the cell.
- Carbohydrates are organic molecules that contain equal amounts of carbon (C) and H_2O. Carbohydrates can be attached to proteins (glycoproteins) or fatty acids (glycolipids) and are critically important for the production and storage of cellular and body energy. The breakdown of glucose to generate energy, or glycolysis, can occur in the presence or absence of O_2 (aerobically or anaerobically). The net production of ATP during aerobic glycolysis is 19 times higher than anaerobic glycolysis.
- Fatty acids are carboxylic acids with extended hydrocarbon chains. They are an important energy source for cells and fatty acid derivatives—including triglycerides, phospholipids, and sterols—have additional important cellular applications.

MULTIPLE-CHOICE QUESTIONS

For all questions, select the single best answer unless otherwise directed.

1. The membrane potential of a particular cell is at the K^+ equilibrium. The intracellular concentration for K^+ is at 150 mmol/L and the extracellular concentration for K^+ is at 5.5 mmol/L. What is the resting potential?
   A. −70 mV
   B. −90 mV
   C. +70 mV
   D. +90 mV
2. The difference in concentration of H^+ in a solution of pH 2.0 compared with one of pH 7.0 is
   A. 5-fold
   B. 1/5 as much
   C. 10^5-fold
   D. 10^{-5} as much
3. Transcription refers to
   A. the process where an mRNA is used as a template for protein production.
   B. the process where a DNA sequence is copied into RNA for the purpose of gene expression.
   C. the process where DNA wraps around histones to form a nucleosome.
   D. the process of replication of DNA prior to cell division.

4. The primary structure of a protein refers to
   A. the twist, folds, or twist and folds of the amino acid sequence into stabilized structures within the protein (ie, α-helices and β-sheets).
   B. the arrangement of subunits to form a functional structure.
   C. the amino acid sequence of the protein.
   D. the arrangement of twisted chains and folds within a protein into a stable structure.
5. Fill in the blanks: Glycogen is a storage form of glucose. _____ refers to the process of making glycogen and _____ refers to the process of breakdown of glycogen.
   A. Glycogenolysis, glycogenesis
   B. Glycolysis, glycogenolysis
   C. Glycogenesis, glycogenolysis
   D. Glycogenolysis, glycolysis
6. The major lipoprotein source of the cholesterol used in cells is
   A. chylomicrons.
   B. intermediate-density lipoproteins (IDL).
   C. albumin-bound free fatty acids.
   D. low-density lipoproteins (LDL).
   E. high-density lipoproteins (HDL).
7. Which of the following produces the most high-energy phosphate compounds?
   A. Aerobic metabolism of 1 mol of glucose
   B. Anaerobic metabolism of 1 mol of glucose
   C. Metabolism of 1 mol of galactose
   D. Metabolism of 1 mol of amino acid
   E. Metabolism of 1 mol of long-chain fatty acid
8. When LDL enters cells by receptor-mediated endocytosis, which of the following does not occur?
   A. Decrease in the formation of cholesterol from mevalonic acid
   B. Increase in the intracellular concentration of cholesteryl esters
   C. Increase in the transfer of cholesterol from the cell to HDL
   D. Decrease in the rate of synthesis of LDL receptors
   E. Decrease in the cholesterol in endosomes

ANSWER: CLINICAL CONCEPT CHECK 1–1

The likely diagnosis and cause are deep vein thrombosis and acute pulmonary embolism, a condition resulting from a blood clot in her leg moving through the veins to her lung. The clot (thromboemboli) in her legs causes her feet to swell and leg pain, and the clot in her lung causes short of breath. The best treatment for edema includes reversing the underlying disorder. Thus, the patient is treated with an anticoagulant to resolve the blood clots in her leg and lung. Furthermore, the patient is asked to wear compression stockings to improve her skin swelling or edema in her lower legs, ankles, and feet.

ANSWER: CLINICAL CONCEPT CHECK 1–3

Based on a consensus statement published by the American Diabetes Association, diagnostic features of hyperosmolar coma or hyperosmolar hyperglycemic syndrome include high plasma glucose level (≥600 mg/dL), high serum osmolality (≥320 mOsm/kg), significant dehydration (up to an average of 9 L), serum pH greater than 7.30, high bicarbonate concentration (>18 mEq/L), small or absent urine, and slight ketonuria and low to absent ketonemia.