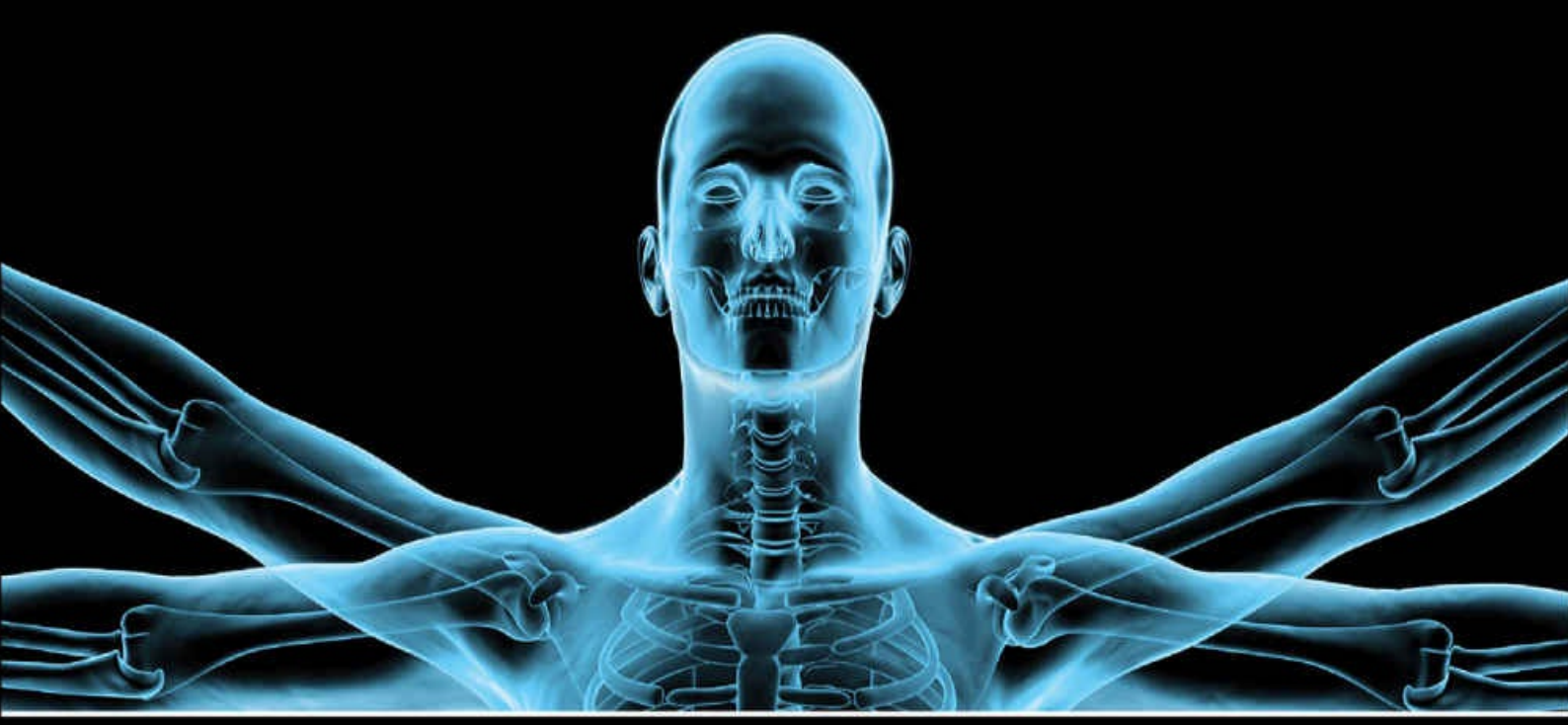

GANONG'S MEDICAL PHYSIOLOGY EXAMINATION & BOARD REVIEW

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Ganong's Medical Physiology Examination & Board Review

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Dedication

This volume is dedicated to William Francis (“Fran”) Ganong, renowned physiologist and neuroendocrinologist. From the first edition in 1963, until the 22nd, he was the sole author of *Review of Medical Physiology*. At the time of his death in 2007, it was one of the most widely used physiology textbook in the world, and it retains an intensely loyal following. His dedication to the volume was legendary, and he was well known for always carrying index cards at his long-term institution, the University of California, San Francisco, where he was a faculty member for almost 50 years and chaired the Department of Physiology from 1970 to 1987. The cards would be used to gather facts from colleagues and visiting speakers, and the facts would be accumulated to inform the next edition of his text—remarkably, completed without fail every 2 years. It is fitting that this new derivative of his life-long work will serve to educate new generations of medical and other health professional students.

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Preface

We have been gratified by the response we have received since taking over the helm of *Ganong's Review of Medical Physiology* with the 23rd edition, and now with two additional editions under our belt. It has been our goal to reorganize and update this venerable resource, while maintaining the features of the book that gave it such an important place in the worldwide marketplace for physiology texts for the 22 editions produced by the extraordinary Professor Fran Ganong. We have paid particular attention to overhauling the graphical aspects of the volume to aid in consistency among chapters and to take advantage of its new full-color format and have added new pedagogical features, such as clinical correlations and therapeutic highlights. Throughout our endeavors to uphold Professor Ganong's unique perspective we have noticed that the book's comprehensive nature reduces its utility as a tool to review physiology content in preparation for Step 1 of the United States Medical Licensing Exam (USMLE). We also felt that the current edition could be improved with supplemental resources with which students can assess their own mastery of the content.

With these limitations in mind, we are pleased to present this companion title, *Ganong's Medical Physiology Examination & Board Review*. Our primary goal has been to streamline the text of the "parent" volume for ease of review, retaining only the most high-yield concepts and illustrations. We have specifically reworked the self-study questions from the original book so that they are consistent with the "clinical vignette" format found in the USMLE and have added many additional questions. In fact, this new book has more than 350 questions to test basic physiology knowledge in an applied context. Finally, every question carries a comprehensive explanation of why the right answer is in fact correct and why the distractors are wrong, further enhancing conceptual understanding of physiology rather than simply reinforcing rote memorization. With these new features, this companion volume represents a robust resource for USMLE preparation.

This new volume also introduces a change in the authorship team. While Professor Heddwen Brooks will continue to contribute to the parent volume, other commitments precluded her involvement in the current project. We are very fortunate to have been able to recruit Professor Jane Reckelhoff to the author group. Janie is an acclaimed teacher of medical and graduate students at the University of Mississippi Medical Center and brings a wealth of experience in the areas of renal, cardiovascular, and gender-related physiology research to our group. Janie's involvement, furthermore, means that three past presidents of the American Physiological Society are now included among the book's authors—perhaps a record for a physiology text.

We hope that a new generation of students will benefit from *Ganong's Medical Physiology Examination & Board Review*—either in conjunction with *Ganong's Review of Medical Physiology*, or as a standalone resource. We also hope that the late Professor Ganong would have been pleased with this evolution of the text that became his life's work.

SECTION I CELLULAR & MOLECULAR BASIS FOR MEDICAL PHYSIOLOGY

The detailed study of physiologic system structure and function has its foundations in physical and chemical laws and the molecular and cellular makeup of each tissue and organ system. This first section provides an overview of the basic building blocks that provide the important framework for human physiology. It is important to note here that these initial sections 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.

In the first part 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 building blocks, basic principles, and human physiology. These basic principles are followed up with a discussion of the generic cell and its components.

In the second part of this introductory section, we take a cellular approach to lay 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 physiology 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 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 available. Students who are intrigued by the overview provided in this first section are encouraged to visit such texts for a more thorough understanding of these basic principles.

CHAPTER

1

General Principles & Energy Production in Medical Physiology

OBJECTIVES

After studying this chapter, you should be able to:

- Define units used in measuring physiologic 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: nucleotides, amino acids, carbohydrates, and fatty acids.
- Understand higher-order structures of the basic building blocks: DNA, RNA, proteins, and lipids.
- Understand the basic contributions of the basic building blocks to cell structure, function, and energy balance.

INTRODUCTION

In humans and other vertebrate animals, specialized cell groups form into organs and include 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. While 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 focuses on a review of basic biophysical and biochemical principles and the introduction of the molecular building blocks that contribute to cellular physiology.

■ GENERAL PRINCIPLES

THE BODY AS ORGANIZED "SOLUTIONS"

The cells that make up the bodies of all, but the simplest multicellular animals are exposed to **extracellular fluid (ECF)** enclosed within the integument of the animal. Cells take up O_2 and nutrients from this fluid, and they discharge metabolic waste products into it. The composition of ECF closely resembles that of the primordial oceans in which, presumably, all life originated.

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 plasma and the cellular elements of the blood fill the vascular system, and together they constitute the **total blood volume.** The interstitial fluid is that part of the ECF that is outside the vascular and lymph systems, bathing the cells. About one-third of the **total body water** is extracellular; the remaining two-thirds is intracellular **(intracellular fluid).** 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 this water is shown in **Figure 1–1A**. Flow between these compartments is tightly regulated.

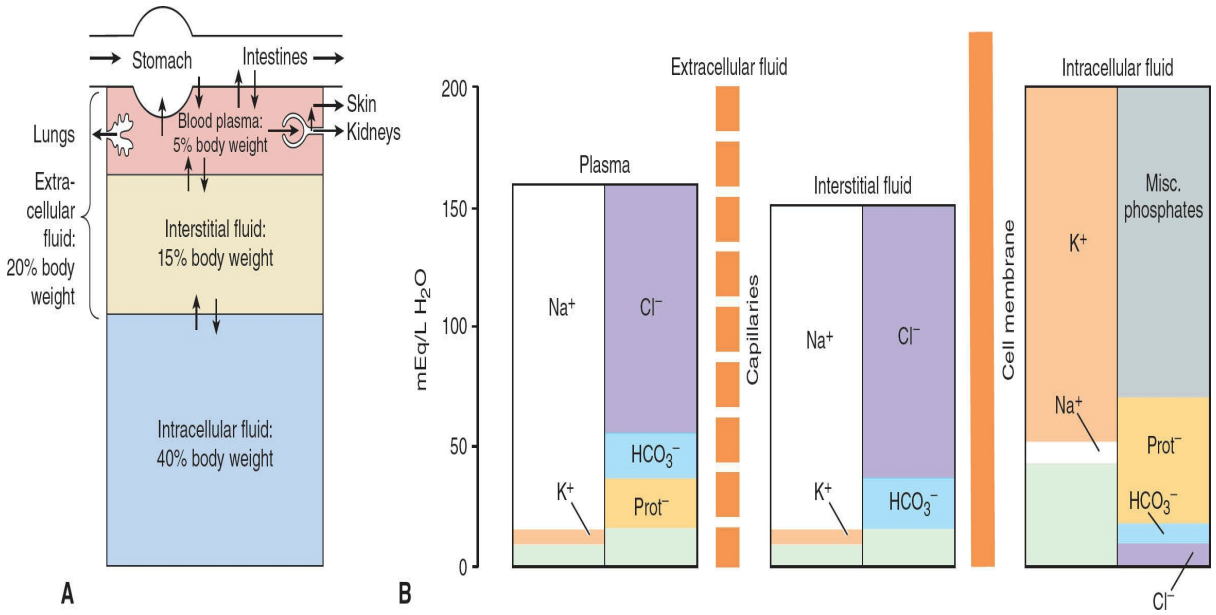

FIGURE 1–1 Organization of body fluids and electrolytes into compartments. (A) Body fluids can be divided into intracellular and extracellular fluid compartments (ICF and ECF, respectively). Their contribution to percentage body weight (based on a healthy young adult male; slight variations exist with 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.

WATER, ELECTROLYTES, & ACID/BASE

The water molecule (H_2O) is an ideal solvent for physiologic 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 layperson's terms, H_2O is an excellent biologic 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**)**.

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. 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 1–1**)**. 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.

CLINICAL BOX 1–1

Acid–Base Disorders

Excesses of acid (acidosis) or base (alkalosis) exist when the blood 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. 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 root cause. Bicarbonate 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.

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 physiologic compounds, most acids or bases are considered "weak"; that is, they contribute or remove relatively few H^+ from 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 constant despite the addition of considerable quantities of acid or base. Of course, there are a number of buffers at work in biologic 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 biologic 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. With some mathematical rearrangement, this can be written in a more conventional form known as the **Henderson-Hasselbalch equation:** $pH = pK_a + \log [A^-]/[HA]$, where pH is the –log of $[H^+]$ and pK_a is the –log of the above defined constant. 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 (eg, $[A^-] = [HA]$, $pH = pK_a$). Similar equations can be set up for weak bases. Important biologic buffers include carbonic acid, phosphates, and proteins.

DIFFUSION & OSMOSIS

Diffusion is the process by which a gas or a substance in a solution expands, because of the motion of its particles, to fill all the available volume. The particles (molecules or atoms) of a substance dissolved in a solvent are in continuous random movement. 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, 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 is directly proportional to the cross-sectional area across which diffusion is taking place and the **concentration or chemical gradient,** and can be represented as **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 Δc/Δx is the concentration gradient. The minus sign indicates the direction of diffusion. When considering movement of molecules from a higher to a lower concentration, Δc/Δx is negative, so multiplying by –DA gives a positive value. Diffusion is a major force affecting the distribution of water and solutes in the body.

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 1–2)**. 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.** 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.

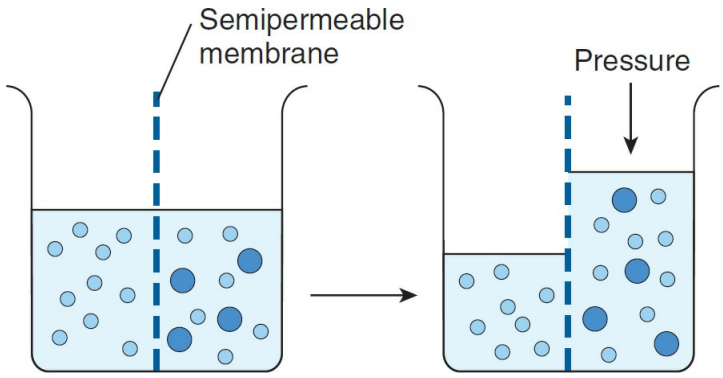

FIGURE 1–2 Diagrammatic representation of osmosis. Water molecules are represented by small open circles, and solute molecules by large solid circles. In the diagram on the left, water is placed on one side of a membrane permeable to water but not to solute, and an equal volume of a solution of the solute 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 depends on the number rather than the type of particles in a solution. 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 biologic solutions, the milliosmole (mOsm; 1/1000 of

1 Osm) is most 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. However, 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. 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 osmolality is expressed in milliosmoles per liter (of water). Note that although a homogeneous solution contains osmotically active particles that 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. The osmolality might be expected to be higher than this, because the sum of all the cation and anion equivalents in plasma is over 300 mOsm/L. However, 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 nearly **isosmotic;** that is, they are in osmotic equilibrium. The term **tonicity** is used to describe the osmolality of a solution of impermeable particles relative to plasma. Solutions that have the same tonicity as plasma are said to be **isotonic; hypertonic** and **hypotonic** refer to higher or lower tonicities as plasma, respectively. 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 across cell membranes 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 can move across the plasma membrane, and can be metabolized, so the net effect is that of infusing a hypotonic solution.

CLINICAL BOX 1–2

Plasma Osmolality & 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 osmolality; however, these can be overwhelmed under certain pathologies. Hyperosmolality can cause coma (hyperosmolar coma). Because of the predominant role of the major solutes and the deviation of plasma from an ideal solution, one can ordinarily approximate the plasma osmolality 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 osmolality (measured by freezing-point depression) that greatly exceeds the value predicted by this formula probably 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).

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 1–2)**.

NONIONIC DIFFUSION, DONNAN EFFECT & NERNST POTENTIAL

Some weak acids and bases are quite soluble in cell membranes in the undissociated form, whereas they cannot cross membranes in the 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.**

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. The **Gibbs–Donnan equilibrium states** that in the presence of a nondiffusible ion, the diffusible ions distribute themselves so that at equilibrium their concentration ratios are equal. This 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 fluid, and because animal cells have flexible walls, osmosis would make them swell and eventually rupture if it were not for **Na,**

K ATPase pumping ions back out of cells. Thus, normal cell volume and pressure depend on Na, K ATPase. Second, because at equilibrium the distribution of permeant ions across the membrane is asymmetric, an electrical difference exists across the membrane whose magnitude can be determined by the **Nernst equation** (see further). Third, because there are more proteins in plasma than in interstitial fluid, there is a Donnan effect on ion movement across the capillary wall.

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

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

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 be invoked to explain the distribution of Cl^- across the membrane.

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.

A similar equilibrium potential can be calculated for K^+ (E_K; Table 1–1). In this case, the concentration gradient is outward and the electrical gradient inward. In mammalian spinal motor neurons E_K is –90 mV. Because the resting membrane potential is –70 mV, there is somewhat more K^+ in the neurons that 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 concentration of Na^+ and K^+ remain constant because of selective permeability and because of 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).

The distribution of ions across the cell membrane and the nature of this membrane provide 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 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. The most important high-energy phosphate compound is **adenosine triphosphate (ATP).** This ubiquitous molecule 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.

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

BIOLOGIC 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.** Biologic 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.

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 details). Ninety percent of the O_2 consumption in the basal state is mitochondrial, and 80% of this 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, 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 1–3)**. These structures are bound to ribose or 2-deoxyribose to complete the nucleoside. When inorganic phosphate is added to the nucleoside, a **nucleotide** is formed. Nucleosides and nucleotides form the backbone for RNA and DNA, as well as a variety of coenzymes and regulatory molecules of physiologic 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.

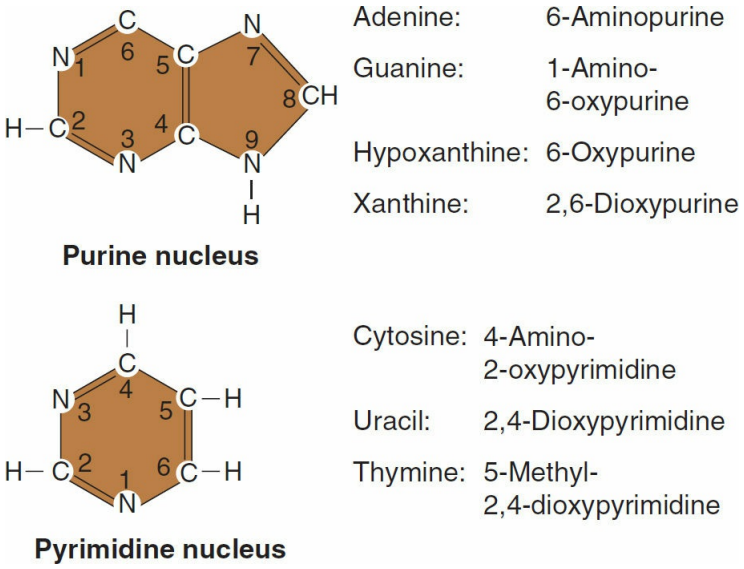

FIGURE 1–3 Principal physiologically important purines and pyrimidines. Purine and pyrimidine structures are shown next to representative molecules from each group. Oxypurines and oxypyrimidines may form enol derivatives (hydroxypurines and hydroxypyrimidines) by migration of hydrogen to the oxygen substituents.

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

DNA

DNA is found in the cell nuclei and in mitochondria. It is made up of two extremely long nucleotide chains containing the bases adenine (typically abbreviated in sequence by the letter “A”), guanine (G), thymine (T), and cytosine (C). The chains are bound together by hydrogen bonding between the bases, with adenine bonding to thymine and guanine to cytosine. This stable association forms a double-helical structure. 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. The protein encoded by a single gene may be subsequently divided into several different physiologically active proteins. The basic structure of a typical eukaryotic gene is shown in diagrammatic form in Figure 1–4. It is made up of a strand of DNA that includes coding and noncoding regions. In eukaryotes 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′> or 3′> regions are **regulatory elements,** which include enhancer and silencer sequences. Each gene can have multiple regulatory sites. 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.

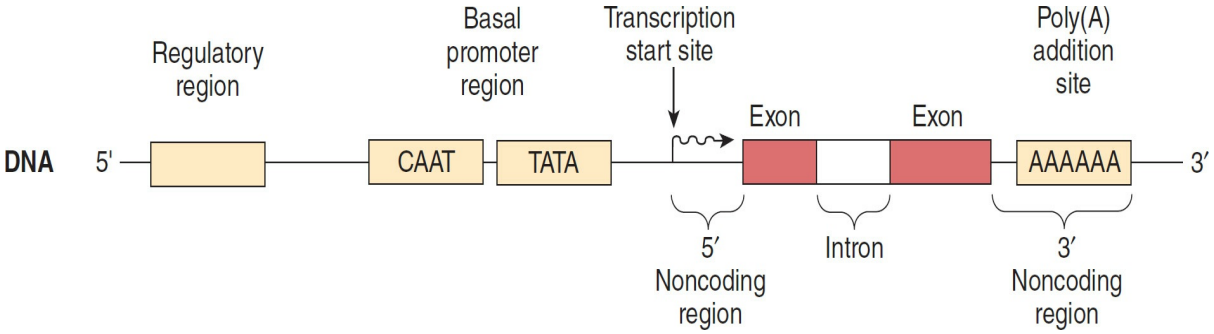

FIGURE 1–4 Diagram of the components of a typical eukaryotic gene. The region that produces introns and exons is flanked by noncoding regions. The 5′-flanking region contains stretches of DNA that interact with proteins to facilitate or inhibit transcription. The 3′-flanking region contains the poly(A) addition site. (Modified with permission from Murray RK et al: *Harper's Biochemistry*, 28th ed. New York, NY: McGraw-Hill; 2009.)

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. 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. 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 1–5). 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 G_2 is marked by chromosome condensation and the beginning of mitosis (M stage).

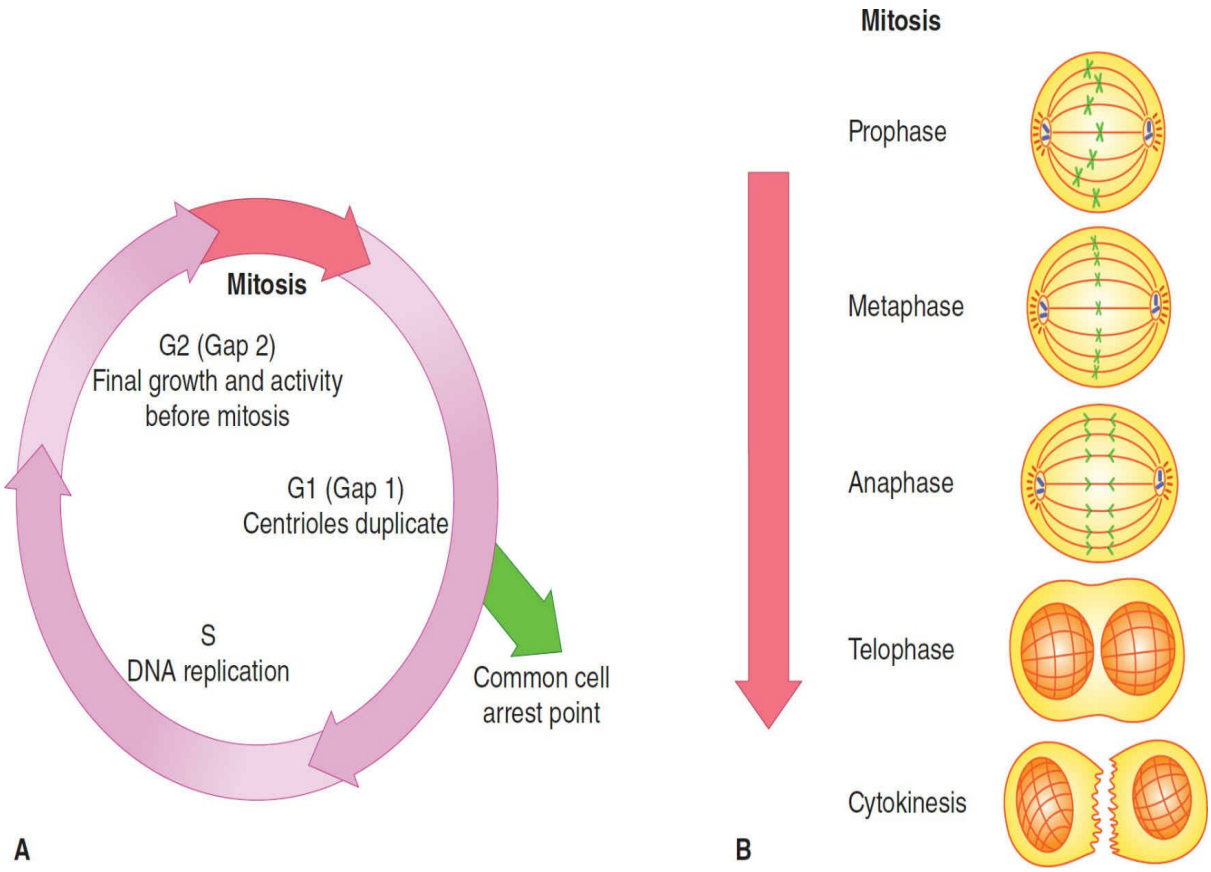

FIGURE 1–5 Sequence of events during the cell cycle. (A) Immediately following mitosis (M) the cell enters a gap phase (G1). At this point many cells will undergo cell arrest. G1 is followed by a DNA synthesis phase (S) a second gap phase (G2) and back to mitosis. **(B)** Stages of mitosis are highlighted.

In germ cells, reductive 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.

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** in place of thymine, and its sugar moiety is ribose rather than 2′>-deoxyribose. 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 includes several unique steps. 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 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 1–6**. 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 roles for these small RNAs will continue to expand as research into their function continues.

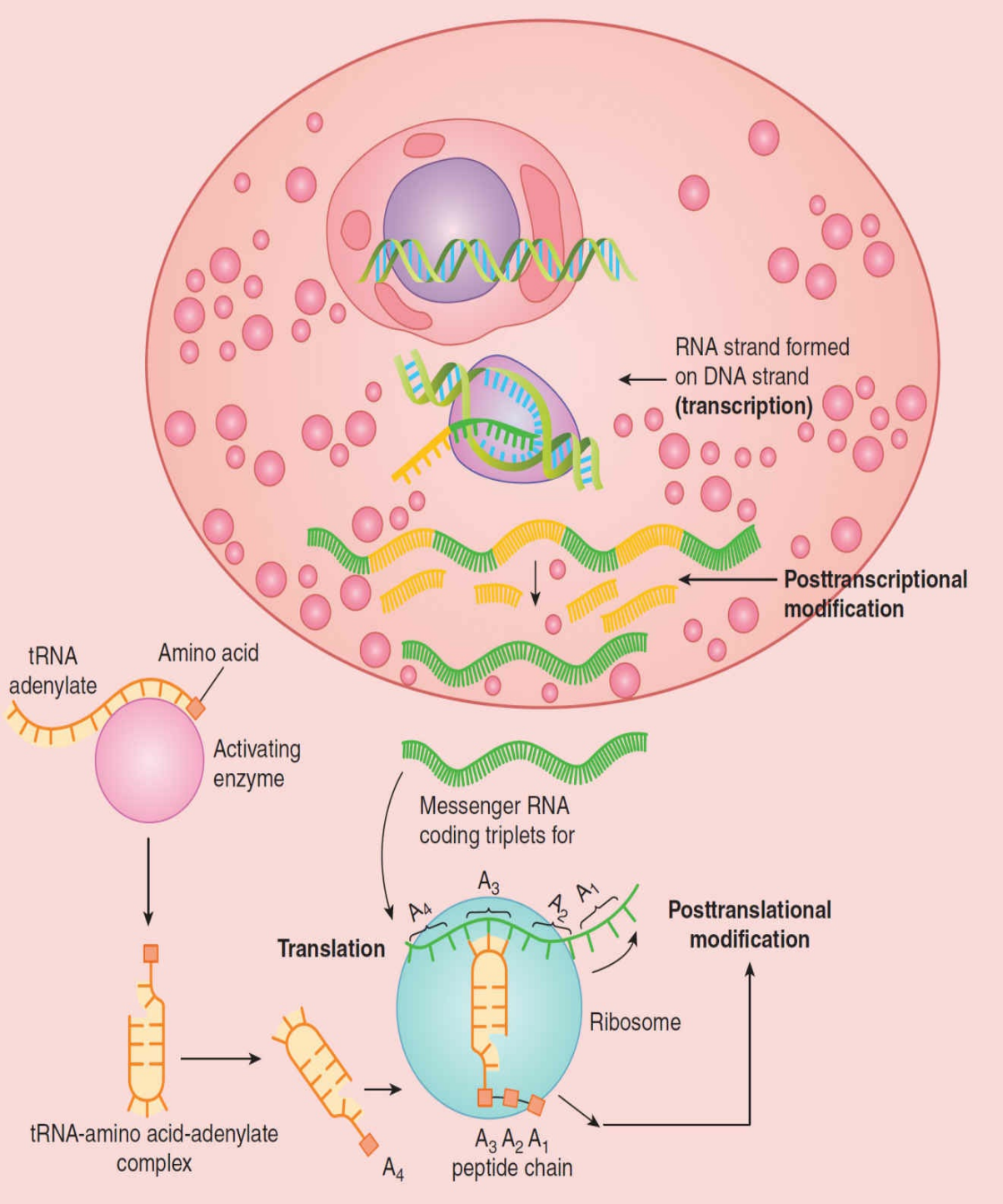

FIGURE 1–6 Diagrammatic outline of transcription to translation. In the nucleus, a messenger RNA is produced from the DNA molecule. This messenger RNA is processed and moved to the cytosol where it is presented to the ribosome. It is at the ribosome where charged tRNA match up with their complementary 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.

■ 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. Various other important amino acids such as ornithine, 5-hydroxytryptophan, L-dopa, taurine, and thyroxine (T_4) occur 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 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
Alanine (Ala, A)	Aspartic acid (Asp, D)
Valine (Val, V)	Asparagine (Asn, N)
Leucine (Leu, L)	Glutamine (Gln, Q)
Isoleucine (Ile, I)	Glutamic acid (Glu, E)
Hydroxyl-substituted amino acids	γ-Carboxyglutamic acid[b] (Gla)
Serine (Ser, S)	Amino acids with side chains containing basic groups
Threonine (Thr, T)	**Arginine**[c] (Arg, R)
Sulfur-containing amino acids	**Lysine** (Lys, K)
Cysteine (Cys, C)	Hydroxylysine[b] (Hyl)
Methionine (Met, M)	**Histidine**[c] (His, H)
Selenocysteine[a]	Imino acids (contain imino group but no amino group)
Amino acids with aromatic ring side chains	Proline (Pro, P)
Phenylalanine (Phe, F)	4-Hydroxyproline[b] (Hyp)
Tyrosine (Tyr, Y)	3-Hydroxyproline[b]
Tryptophan (Trp, W)	

Those in bold type are the nutritionally 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 maintenance of nitrogen balance, but are needed for normal growth.

Most ingested proteins are digested into their constituent amino acids before absorption. The body's proteins are being continuously hydrolyzed to amino acids and resynthesized. The turnover rate of endogenous proteins averages 80–100 g/d, 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 1–7)**.

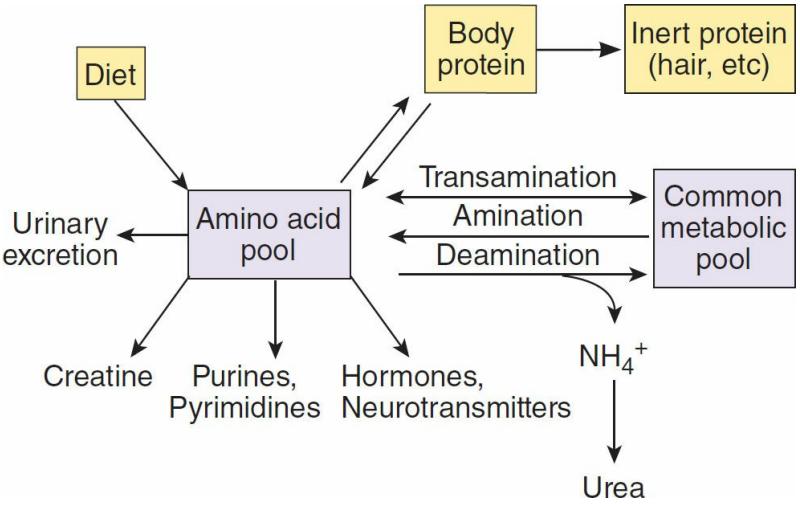

FIGURE 1–7 Amino acids in the body. There is an extensive network of amino acid turnover in the body. Boxes represent large pools of amino acids and some of the common interchanges are represented by arrows. Note that most amino acids come from the diet and end up in protein; however, a large portion of amino acids are interconverted and can feed into and out of a common metabolic pool through amination reactions.

PROTEINS & PROTEIN SYNTHESIS

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. In addition, some proteins contain carbohydrates (glycoproteins) and lipids (lipoproteins). Smaller chains of amino acids are called **peptides** or **polypeptides.** 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. Common secondary structures include the α-helix and β-sheet. 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.

The process of protein synthesis, **translation,** is the conversion of information encoded in mRNA to a protein (Figure 1–6). 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, 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. 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 bases, and each codon stands for a particular amino acid.

Translation typically starts in the ribosomes with an AUG codon for methionine. The amino 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. Translation stops at one of three stop, 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 biologic 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.** Chaperones 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** 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. The ribosome also binds, and the signal peptide leads the growing peptide chain into the cavity of the endoplasmic reticulum **(Figure 1–8)**. 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.

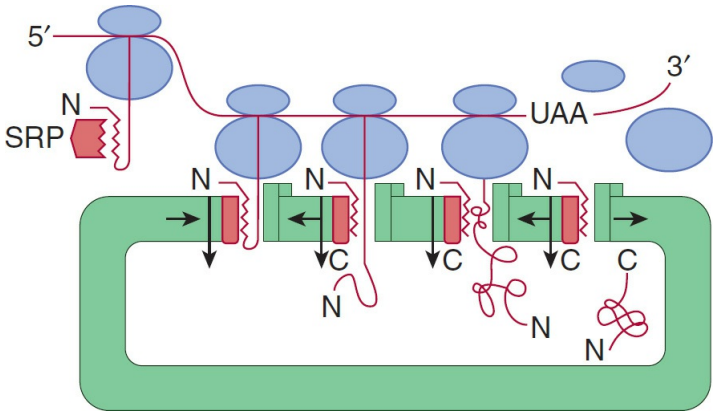

FIGURE 1–8 Translation of protein into the endoplasmic reticulum according to the signal hypothesis. The ribosomes synthesizing a protein move along the mRNA from the 5′ to the 3′ end. When the signal peptide of a protein destined for secretion, the cell membrane, or lysosomes emerges from the large 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. N, amino end of protein; C, carboxyl end of protein. (Reproduced with permission from Perara E, Lingappa VR: Transport of proteins into and across the endoplasmic reticulum membrane. In: Das RC, Robbins PW: *Protein Transfer and Organelle Biogenesis.* Academic Press, 1988)

UBIQUITINATION & PROTEIN DEGRADATION

Like protein synthesis, protein degradation is a carefully regulated, complex process. Abnormally produced proteins (up to 30% of newly produced proteins) and aged normal proteins 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 across 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 cellular signaling pathways. 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.

CATABOLISM OF AMINO ACIDS

The short-chain fragments produced by amino acid, carbohydrate, and fat catabolism are very similar and form a **common metabolic pool.** These fragments can also enter the citric acid cycle where 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. For example, alanine + α-ketoglutarate $\rightleftharpoons$ pyruvate + glutamate. Alternatively, **oxidative deamination** of amino acids occurs in the liver. In this two-step reaction, an imino acid is formed by dehydrogenation, and the imino acid is then hydrolyzed to the corresponding keto acid, with production of NH_4^+: amino acid + $NAD^+ \rightarrow$ imino acid + NADH + H^+; imino acid + $H_2O \rightarrow$ keto acid + NH_4^+. 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 (urea cycle; **Figure 1–9)**. The NH_4^+ enters the mitochondria and forms carbamoyl phosphate where it is transferred to ornithine to form citrulline. The enzyme involved is ornithine carbamoyltransferase. Citrulline is converted to arginine, after which urea is split off and ornithine is regenerated. 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. Congenital deficiency of ornithine carbamoyltransferase can also lead to NH_3 intoxication.

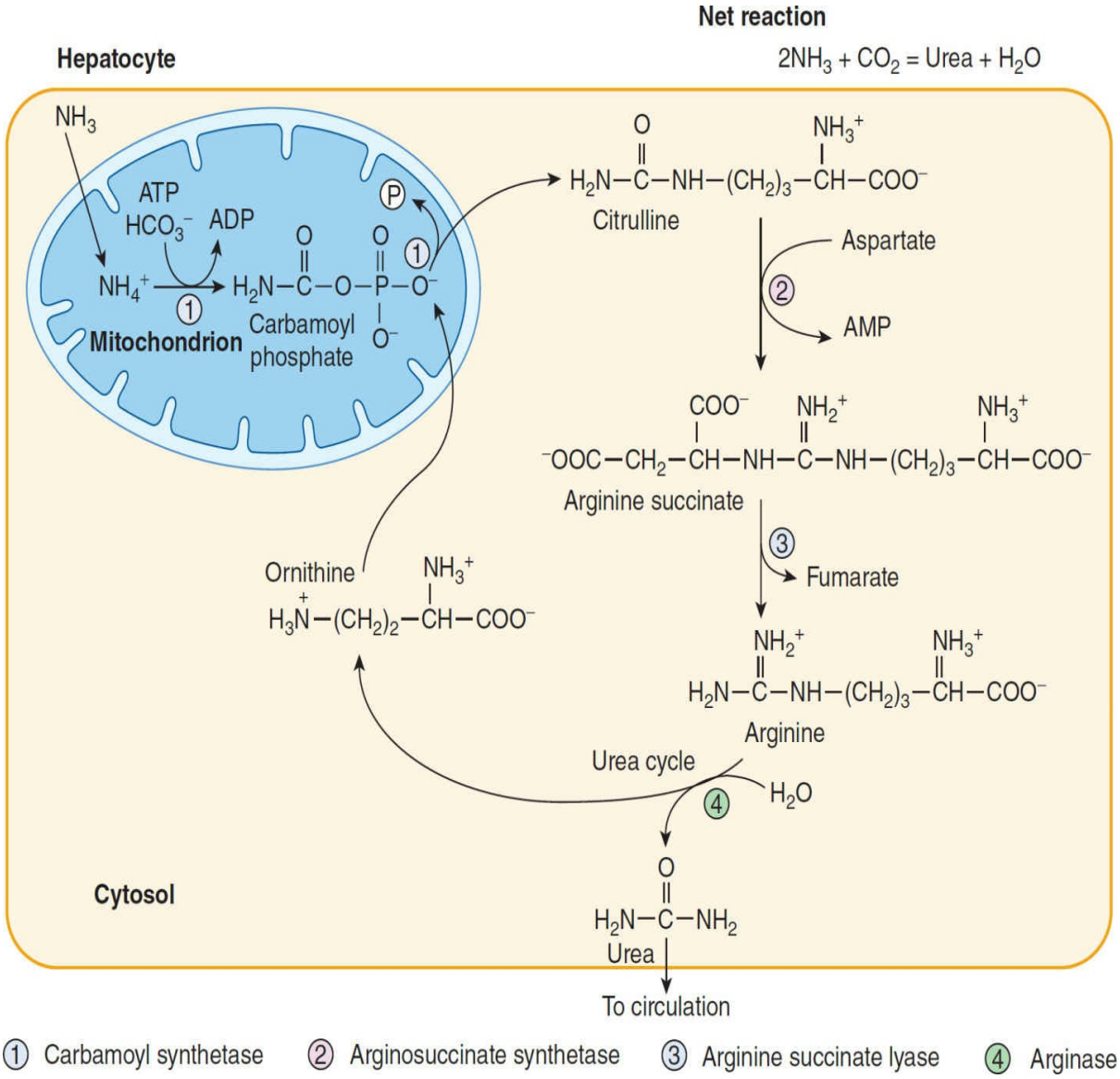

FIGURE 1–9 Urea cycle. The processing of NH_3 to urea for excretion contains coordinative steps in both the cytosol and the mitochondrion of a hepatocyte. Note that the production of carbamoyl phosphate and its conversion to citrulline occurs in the mitochondria, whereas other processes are in the cytoplasm.

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 roles (eg, inositol 1,4,5 trisphosphate acts as a cellular signaling molecules) 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. The principal product of carbohydrate digestion and the principal circulating sugar is glucose. The normal 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 glucose enters cells, it is normally phosphorylated by **hexokinase**, forming glucose-6-phosphate. Glucokinase found in the liver has greater specificity for glucose, and 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 (**Embden–Meyerhof pathway**) or via oxidation and decarboxylation to pentoses (**direct oxidative pathway; hexose monophosphate shunt or pentose phosphate pathway)**. Pyruvate is converted to acetyl-CoA. Interconversions between carbohydrate, fat, and protein include conversion of glycerol from fats to dihydroxyacetone phosphate and conversion of a number of amino acids with carbon skeletons resembling intermediates in the Embden–Meyerhof pathway and citric acid cycle 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.

CITRIC ACID CYCLE

The **citric acid cycle** (Krebs cycle, tricarboxylic acid cycle) is 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 1–10)**. Four pairs of H atoms are transferred to the flavoprotein–cytochrome chain, producing 12 ATP and 4 H_2O, of which 2 H_2O is used in the cycle. The citric acid cycle is the common pathway for oxidation to CO_2 and H_2O of 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.