CHAPTER 1

FOUNDATIONS OF THE HUMAN BODY

HERE'S WHERE YOU ARE GOING:

1. The human body is composed in some fashion of 27 of the more than 100 existing elements.
2. The basic unit of life from a nutritional perspective is the cell.
3. Cell components have specialized functions, all of which affect nutritional utilization.
4. Cell proteins have specialized functions, including serving as enzymes, receptors, transporters, and hormones.
5. Not all tissues are created equal. There are more than 200 cell types with the same DNA but with different functions and nutrient requirements.

Introduction

Undeniably, nutrition is of primary importance to the anatomic and physiologic development and maintenance of the human body. This complex multicellular entity consists of organ systems and tissue working together to support growth, maturation, defense, and reproduction. From an evolutionary perspective, humans developed into bipedal primates endowed with enormously expanded cerebral hemispheres, particularly the frontal lobes, which are responsible for intelligent behavior and muscular dexterity. These characteristics allow humans to move agilely in various directions, investigate their environment, and understand and learn complex behaviors. They also allow humans, unlike other animals, the potential to investigate and comprehend the importance of their own nutrition. In a general sense, humans are inhalation units and food processors, combustion units for energy molecules as well as storage facilities for excessive energy, possessing waste removal and defensive systems, internal and external communication systems, locomotive capabilities, and reproductive capabilities. All of these functions are founded on or influenced by nutritional intake.

Comprehension as to how to nourish the human body demands at the very least a basic understanding of just what it is that needs to be nourished. But where does one begin this understanding? Perhaps the most obvious starting point is at the cellular level. Although it is indeed easier for humans to think of themselves as a single unit, the truth of the matter is that a human being is a compilation of some 60 to 100 trillion **cells**. Every one of these cells is a living entity engaging in homeostatic operations to support self-preservation, while in some manner concurrently engaging in homeostatic mechanisms for the human body as a whole. Each cell is metabolically active, and thus requiring nourishment, while at the same time producing waste. Therefore, nutrition cannot merely be defined as the study of the nourishment of the human body; rather, it is the nourishment of individual cells and the tissues and organs they make up. An understanding of nutrition also needs to go beyond the living or viable portions of the body to recognize the building blocks of cells themselves—namely, elements and molecules.

Elements and Molecules

Of the more than 100 elements known at this time, the human body employs about 27. Oxygen is the most abundant element in the human body, accounting for about 63% of its mass. Carbon (18%), hydrogen (9%), and nitrogen (3%) follow oxygen in decreasing order of abundance (**Table 1.1**). Carbon, hydrogen, oxygen, and nitrogen atoms are foundations for the most abundant types of molecules in the body, namely, water, proteins, lipids, carbohydrates, and nucleic acids. Water typically accounts for about 55% to 65% of human mass, whereas proteins and lipids collectively may contribute about 30% to 45%. Finally, nucleic acids, carbohydrates, and other organic molecules contribute about 1% or so to human mass. The remaining portion of the body, about 5%, is largely composed of minerals (**Table 1.2**).

With the exception of water, the major types of molecules forming the human body are complex and largely constructed of simpler molecules. For example, proteins are composed of **amino acids** linked by peptide bonds.

TABLE 1.1 Elements of the Human Body

Major Elements[a]				Trace Elements[b]	
Oxygen	63.0%	Potassium	0.4%	Silicon	Boron
Carbon	18.0%	Sulfur	0.3%	Aluminum	Selenium
Hydrogen	9.0%	Sodium	0.2%	Iron	Chromium
Nitrogen	3.0%	Chloride	0.1%	Manganese	Cobalt
Calcium	1.5%	Magnesium	0.1%	Fluorine	Arsenic
Phosphorus	1.0%			Vanadium	Molybdenum
				Iodine	Zinc
				Tin	Copper

[a]Percentages indicate the percentage of body mass composed of a particular element.

[b]Each trace element contributes less than 0.01% to total body mass.

TABLE 1.2 Theoretical Contributors to Body Weight for a Lean Man and Woman

Component	Man (%)	Woman (%)
Water	62	59
Fat	16	22
Protein	16	14
Minerals	6	5
Carbohydrate	<1	<1
TOTAL	**100**	**100**

Deoxyribonucleic acid (**DNA**) and ribonucleic acid (**RNA**) are assembled from nucleotides, which themselves are constructed from smaller molecules, namely purine and pyrimidine bases, phosphoric acid, and a carbohydrate (2-deoxy-D-ribose and D-ribose for DNA and RNA, respectively). **Triglycerides** (e.g., triacylglycerol) contain three **fatty acids** esterified to a glycerol molecule, and glucose molecules can be linked together by anhydride bonds to form the carbohydrate storage polymer glycogen.

Cell Structure and Organelles

Although there are over 200 different types of cells in the human body, each performing a unique or somewhat enhanced function, most of the basic structural and operational features are conserved among all cells. This means that although **skeletal muscle** cells and **adipocytes** (fat storage cells) may seem very different in many respects, including primary purpose, color, and shape, the most basic structures and functions of both cell types are virtually the same (**Figure 1.1**). This allows us to discuss cells initially as a single entity, and then to expound the unique or highly specialized functions of specific cells in a later discussion.

Human cells have an average size of 5 to 10 micrometers and were first described using light microscopy. Light microscopy allows an imaging magnification of about 1,500 times. However, it was not until the advent of electron microscopy that the finer detail of cells' **organelles** and ultrastructural aspects were scrutinized. Electron microscopy has the potential to expand imaging magnification up to 250,000 times.

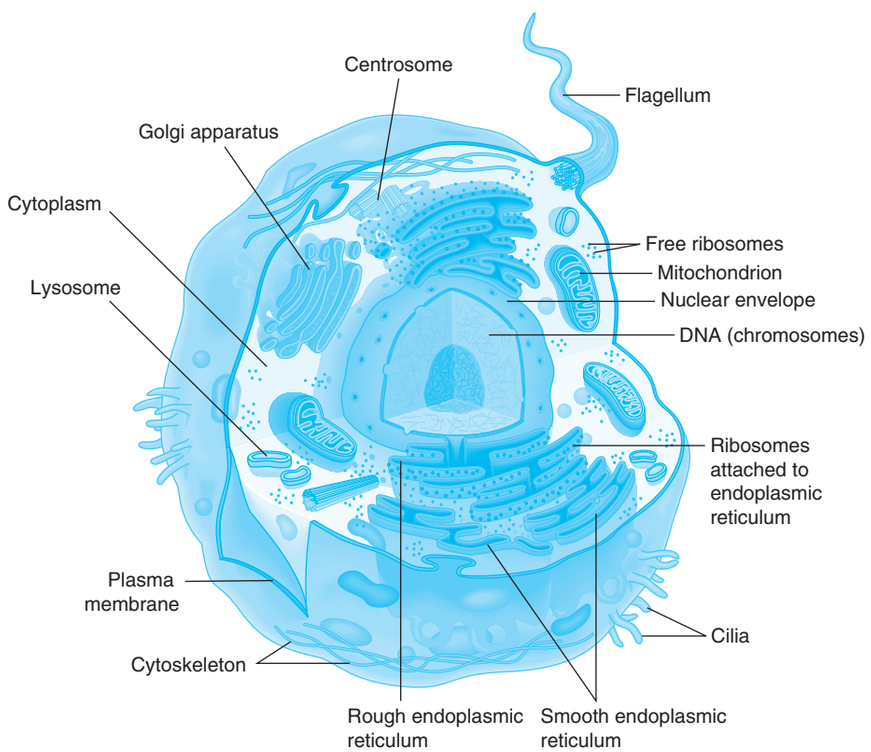


FIGURE 1.1 **General Cell Structure.** The figure shows the plasma membrane, cytoplasm, mitochondria, ribosomes, lysosomes, endoplasmic reticulum, Golgi apparatus, and the nuclear envelope.

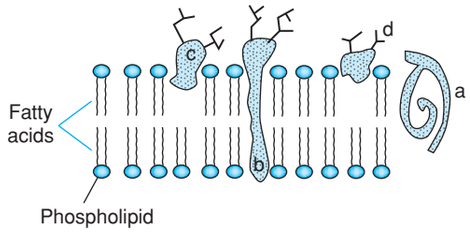


FIGURE 1.2 Membrane Structure: The Fluid Mosaic. A phospholipid bilayer (a) with associated proteins. Transmembrane proteins (b) can extend all the way through the membrane, such as the ion channel displayed. Peripheral proteins (c) are associated with only one side of the bilayer. Carbohydrate extensions (d) from membrane structures form the glycocalyx.

Enveloped in a fluid plasma membrane, the cell can be divided into two major parts: the nucleus and the cytoplasm. The plasma membrane is approximately 7.5 to 10 nanometers thick, and its approximate composition by mass is proteins, 55%; **phospholipids**, 25%; cholesterol, 13%; other lipids, 4%; and carbohydrates, 3%. The plasma membrane is arranged in a lipid bilayer structure, thus making the membrane merely two molecules thick (**Figure 1.2**). Phospholipids and cholesterol make up most of the lipid bilayer and are oriented so that their hydrophilic (water-soluble) portion faces the watery medium of the intracellular and extracellular fluids, and their hydrophobic (water-insoluble) portion faces the internal aspect of the bilayer. The major phospholipids in the plasma membrane can vary among cell types; however, they generally include phosphatidylcholine (lecithin), phosphatidylethanolamine, phosphatidylserine, and sphingomyelin (**Figure 1.3**). Inositol phospholipids are functionally important in **cell signaling** operations; however, their quantitative contribution to plasma membrane lipid mass is relatively small. The hydrophobic inner region of the bilayer provides a transit barrier impermeable to hydrophilic substances such as ions, glucose, amino acids, and urea.

The plasma membrane of a small human cell may contain 10^9 lipid molecules, about half of which are phospholipids. Cholesterol and glycolipids account for most of the remaining lipid. The planar cholesterol molecule is oriented so that its hydrophilic hydroxyl group is directed toward the polar ends of phospholipids and their hydrophobic steroid rings and hydrocarbon tail are directed toward the hydrophobic middle region of the plasma membrane bilayer (**Figure 1.4**). The concentration of cholesterol adds stability to the plasma membrane by preventing phospholipid fatty acid hydrocarbon chains from crystallizing.

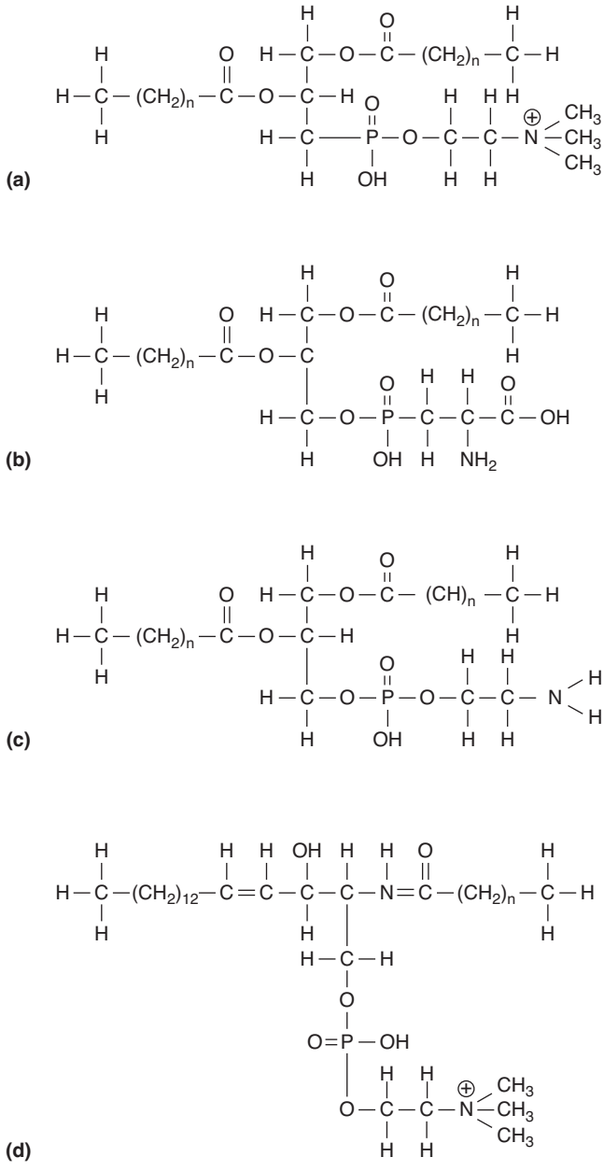


FIGURE 1.3 Phospholipid Molecular Structures. Phosphatidylcholine or lecithin (a), phosphatidylserine (b), phosphatidylethanolamine (c), and sphingomyelin (d).

Proteins are a major component of plasma membrane, accounting for about 55% of its mass. However, with respect to the molecular size differential between membrane proteins and lipids, the ratio of lipid to protein molecules is about 50 to 1. Cell membrane proteins occur either as integral or peripheral proteins that float within the bilayer. Integral, or transmembrane, proteins extend through the plasma membrane and function primarily as

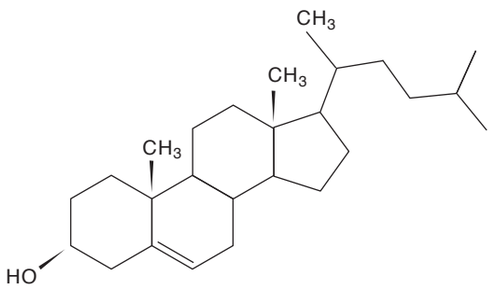


FIGURE 1.4 Cholesterol Molecule. Cholesterol is a planar molecule that enhances the stability of the plasma membrane. It is generally a hydrophobic molecule, with the exception of the hydroxyl group (OH).

ion channels, carriers, active transporters, receptor bases, and enzymes. Typically, the portion of these proteins that extends through the hydrophobic core of the plasma membrane is composed mostly of amino acids with nonpolar side chains. Transmembrane proteins are mostly glycoproteins, with their carbohydrate moiety extending into the extracellular fluid. Peripheral proteins are typically associated with integral membrane proteins on the intracellular side of the plasma membrane, and their function is mostly enzymatic.

Carbohydrates, in the form of polysaccharides attached to plasma membrane proteins (glycoproteins) and lipids (glycolipids), along with proteoglycans make up the glycocalyx (see Figure 1.2). The glycocalyx provides a carbohydrate coat on the extracellular face of the plasma membrane that appears to be involved in receptor activities and cell-to-cell adhesion.

The plasma membrane encloses the cytoplasm, which is composed of the cytosol and organelles. The cytosol is a clear intracellular fluid containing several substances either dissolved, suspended, or anchored within the watery medium. These substances include electrolytes, proteins, glucose and **glycogen**, amino acids, and lipids. The concentration of these intracellular substances can differ tremendously from the extracellular fluid (**Table 1.3**). For example, the extracellular fluid may be 14 times more concentrated with sodium and 10 times less concentrated with potassium in comparison with the intracellular fluid. One function of integral membrane proteins is to pump certain substances against their concentration or diffusion gradients to maintain these differences for physiologic purposes.

Many of the highly specialized operations that take place inside cells occur within membrane-contained organelles. Organelles include the endoplasmic reticulum, Golgi apparatus, lysosomes, peroxisomes, endosomes, and mitochondria. Although most types of cells contain all of these organelles or a highly specialized version, the organelles' contribution to the total cell volume can vary. For example, myocytes (**muscle cells**) contain a rich complement of mitochondria, whereas the total surface area of endoplasmic reticulum in a **hepatocyte** (liver cell) is 30 to 40 times greater than the surface area of the plasma membrane. **Table 1.4** presents general functions associated with different organelles.

TABLE 1.3 Concentration Differences of General Solutes Across the Plasma Membrane[a]

	Intracellular Fluid (mmol/L)	Extracellular Fluid (mmol/L)
Sodium (Na^+)	12	145
Potassium (K^+)	155	4
Hydrogen (H^+)	13×10^{-5}	3.8×10^{-5}
Chloride (Cl^-)	3.8	120
Bicarbonate (HCO_3^-)	8	27
Organic anions (e.g., lactate)	155	trace

[a]Electrolyte concentration across the skeletal muscle plasma membrane.

TABLE 1.4 Overview of Organelle Function

Organelle	Function and Features
Nucleus	Site of most DNA and transcription; site of rRNA production
Mitochondria	Site of most ATP synthesis in cells; some DNA
Lysosomes	Contain acid hydroxylases for digesting most biomolecule types
Endoplasmic reticulum	Synthesizes proteins and lipid substances destined to be exported from cell; site of glucose-6-phosphatase; participates in ethanol metabolism
Golgi apparatus	Further processes molecules synthesized in the endoplasmic reticulum: packaging site for exocytosis-destined molecules; synthesizes some carbohydrates
Peroxisomes	Contain oxidases; participate in ethanol metabolism
Endosomes	Structures produced by the invagination of the cell membrane or Golgi body for degradation or recycling

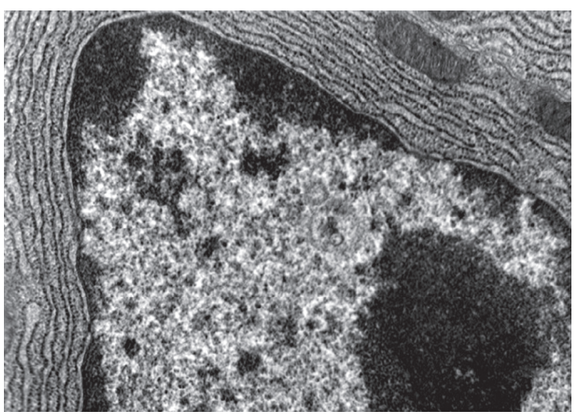
DNA, deoxyribonucleic acid; rRNA, ribosomal ribonucleic acid; ATP, adenosine triphosphate.

Endoplasmic Reticulum

The **endoplasmic reticulum** is a tubular network that is situated adjacent to nuclei. In fact, the space inside the tubular network containing the endoplasmic reticulum matrix is connected to the space in between the two membranes of the nuclear envelope. The membrane of the endoplasmic reticulum is very similar to the plasma membrane, consisting of a lipid bilayer densely embedded with proteins. The endoplasmic reticulum is a major site of molecule formation and metabolic operations within cells.

Visually, the endoplasmic reticulum can be separated into the rough (granular) and smooth (agranular) endoplasmic reticulum due to the presence of ribosomal complexes attached to its outer surface. The electron micrograph in **Figure 1.5** displays the ribosomal studding of the endoplasmic reticulum. The ribosomes of the rough endoplasmic reticulum are the site of synthesis for many proteins. As they are being synthesized, growing protein chains thread into the endoplasmic reticulum matrix, where they can undergo rapid glycosylation as well as cross-linking and folding to form more compact molecules. In general, proteins synthesized by the rough endoplasmic reticulum are destined for either exocytosis or to become part of the plasma or organelle membranes. In contrast, the smooth endoplasmic reticulum is a site of synthesis of several lipid molecules, including phospholipids and cholesterol. Once synthesized, these lipids become incorporated into the endoplasmic reticulum membrane, allowing for regeneration of the membrane lost in the form of **transport** vesicles destined for the Golgi apparatus.

Finally, the endoplasmic reticulum engages in other significant cellular operations. The endoplasmic reticulum of specific cells, such as the parenchyma of the liver and kidneys, contains glucose-6-phosphatase, which liberates glucose from glucose-6-phosphate generated by gluconeogenesis as well as glycogen breakdown for release from the cell. The endoplasmic reticulum is also the site of detoxification of potentially harmful substances such as drugs and alcohol. The cytochrome P450 system is the primary site of detoxification operations in the endoplasmic reticulum.



Courtesy of Louisa Howard, Dartmouth College, Electron Microscope Facility

FIGURE 1.5 Rough Endoplasmic Reticulum. Electron micrograph of rough endoplasmic reticulum surrounding a nucleus (28,000×) showing the ribosomal studding.

Golgi Apparatus

The **Golgi apparatus** is composed of several stacked layers of thin, flat, enclosed vesicles and is located in close proximity to both the nucleus and endoplasmic reticulum. It processes substances produced by the endoplasmic reticulum and also synthesizes some carbohydrates. The carbohydrates include sialic acid and galactose, as well as more complex polysaccharide protein–based molecules such as **hyaluronic acid** and **chondroitin sulfate**. These are part of the proteoglycan component of mucous and glandular secretions, as well as being primary components of the organic matrix of connective tissue such as bone, cartilage, and **tendons**. However, it is the molecule-processing and vesicle-formation activities of the Golgi apparatus that are without doubt its most famous attributes. As molecules, especially proteins, are manufactured in the endoplasmic reticulum, they are transported throughout the tubular system, destined to reach the agranular portion in closest proximity to the Golgi apparatus. At this location, small transport vesicles pinch off and transport these substances to the Golgi apparatus (**Figure 1.6**). The vesicles introduce their cargo to the Golgi apparatus by fusing with its membrane.

Once inside the Golgi apparatus, endoplasmic reticulum–derived molecules, which are primarily proteins, can have more carbohydrate moieties added and become incorporated into highly concentrated packets. Eventually the packets will bud off the Golgi apparatus and diffuse into the cytosol. The packets are then ready to fuse with the plasma membrane to form endosomes (described below) and release their contents into the extracellular space in an exocytotic process. Because of this activity, these packets are often referred to as secretory vesicles or secretory granules. Cells with greater endocrine, exocrine, paracrine, and autocrine activities, such as the pancreas, adrenal glands, and anterior pituitary gland, will show more secretory vesicles when observed with electron microscopy. The contents of these packets may be **hormones**, neurotransmitters, eicosanoids, or ductal secretions. Some of the concentrated packets are not destined for exocytosis, however, because highly specialized buds from the Golgi apparatus become lysosomes.

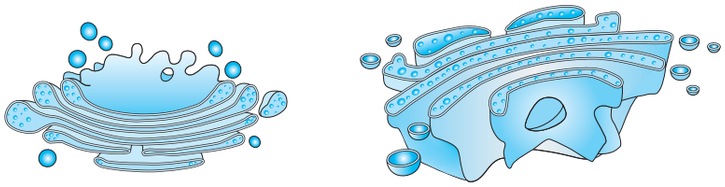


FIGURE 1.6 Golgi Apparatus. Budding of vesicles from the plasma membrane face of the Golgi apparatus. The vesicles generally contain substances that will be secreted from the cell.

Endosomes, Lysosomes, and Peroxisomes

Endosomes are produced by an invagination of the cell membrane to transport a variety of compounds (usually lysosomes) for degradation. These structures may also be produced by the Golgi body. Endosomes can transfer materials to the cell membrane for recycling. A good example of this is in the regulation of low density lipoprotein (LDL). LDL-cholesterol binds to a cell receptor, and the complex is then internalized within the cell in the form of an endosome. The LDL-cholesterol is removed and processed in the lysosome, and the receptor is recycled back to the cell membrane surface for reutilization. These structures are in many ways responsible for sorting materials within the cell to other cellular organelles or components. The mature endosome is approximately 500 nanometers in diameter.

Lysosomes, which are usually between 250 to 750 nanometers in diameter and loaded with hydrolytic enzyme–containing granules, function as an intracellular digestive system. More than 50 different acid hydroxylases have been found in lysosomes and are involved in digesting various proteins, nucleic acids, mucopolysaccharides, lipids, and glycogen. Lysosomes are very important in cells such as macrophages.

Peroxisomes appear to be produced by specialized buddings of the smooth endoplasmic reticulum and contain oxidases that help detoxify potentially harmful substances. Peroxisomes also participate to some degree in ethanol (alcohol) oxidation and the oxidation of long-chain fatty acids.

Mitochondria

Aerobic adenosine triphosphate (ATP) generation takes place in **mitochondria**, self-replicating organelles found in almost every cell type in the human body (see Figure 1.1). Mitochondria can vary in size in different types of cells. In some cells, mitochondria may only be a few hundred nanometers in diameter, whereas in others they may be as large as 1 micrometer in diameter and as long as 7 micrometers in length. The shape of mitochondria can also vary among cell types. For instance, mitochondria are spherical in brown adipose cells, sausage-shaped in muscle cells, and more oval in hepatocytes. The density of mitochondria within a cell type depends primarily on the oxidative energy demands of that cell. For instance, because of their dedication to the synthesis of chemical compounds, hepatocytes contain about 800 mitochondria per cell. Likewise, the high ATP demands of muscle cells also require a rich complement of mitochondria. Mitochondria account for about 25% to 35% and 12% to 15% of cardiac and skeletal myocyte volume, respectively.

Mitochondria tend to be located within cells in areas near organelles with high energy demands. Thus, mitochondria would typically appear in close proximity to the nucleus and ribosomes, where protein synthesis occurs, or near contractile myofibril in muscle cells. Also, triglyceride-rich lipid droplets are typically visualized adjacent to or at least in close proximity to mitochondria.

Mitochondria contain two lipid/protein bilayer membranes that are commonly called the outer membrane and the inner membrane (**Figure 1.7**). The outer membrane is very porous and is largely unfolded, whereas the inner membrane is relatively impermeable and highly

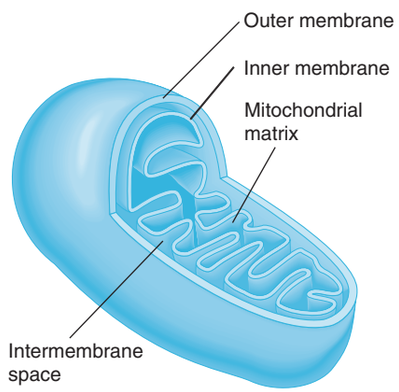


FIGURE 1.7 Mitochondrion. Note the inner and outer mitochondrial membranes.

SPECIAL FEATURE 1.1

Newer Findings on Mitochondrial Diseases

Genetic, metabolic, and dietary events can result in mitochondrial diseases. Mitochondrial diseases may be due to base-pair substitutions in the mitochondrial genome or may involve defects in the nuclear-encoded mitochondrial proteins. The mechanisms or proteins responsible for ferrying some mitochondrial proteins (chaperone proteins) synthesized in the cytoplasm to the mitochondria can also be defective, and the import of such proteins into the mitochondria can be impaired. All of these factors collectively can lead to mitochondrial dysfunction and pathology.

A number of mitochondrial diseases affect skeletal and cardiac muscle and peripheral and central nervous system tissue, particularly the brain, the liver, bone marrow, the endocrine and exocrine pancreas, the kidneys, and the intestines. Kearns-Sayre syndrome is a mitochondrial disease in which deletion of parts of NADH–coenzyme Q reductase (subunits III and IV), all of ATP synthase subunit VI, and part of ATP synthase subunit VIII occurs. The DNA responsible for encoding **cytochrome c oxidase** subunit IV is present, but not the DNA of mitochondria-encoded cytochrome c oxidase subunit II. Another disorder, myoclonus epilepsy with ragged red fibers (MERRF), affects both brain and muscle tissue. This disorder causes a notable decrease in cytochrome c oxidase subunit II protein but not in the mRNA. A child afflicted with Leigh syndrome revealed a disorder involving a nuclear mutation in cytochrome c oxidase, but all subunits were present to lesser degrees.

There have been several reports of defects in cytochrome c oxidase in patients suffering from cardiomyopathy, which is a type of heart disease where the muscle fails to contract. More recently, a copper chaperone protein, called SCO2, was found to be mutated in several forms of fatal infantile cardiomyopathy leading to cytochrome c oxidase deficiency. This protein ferries copper from one protein to SCO2, which inserts copper into the cytochrome c oxidase. Apparently this protein is nonfunctional in some people. In another study, a patient with SCO2 mutations had severe hypertrophic cardiomyopathy that was reversed with copper-histidine supplementation.

SPECIAL FEATURE 1.2

The Birth and Renewal of Mitochondria: Mitochondrial Biogenesis

The number of mitochondria in any given cell is not static. Some cells, such as those in cardiac tissue, have a high number of mitochondria, whereas cells in the brain have a low number. It could be that the heart relies more on fatty acids for energy, thus requiring more mitochondria. The brain, in contrast, requires more glucose to function, and thus does not need as many mitochondria because it does not prefer to use fatty acids as a source of energy. The creation of more mitochondria under selected conditions is called mitochondrial biogenesis. What are the molecular factors that cause mitochondrial biogenesis?

Mitochondria transcription factor A (mtTFA) is a major transcription factor governing mitochondrial DNA replication and transcription during mitochondrial biogenesis. A transcription factor is normally a protein that binds to the promoter of a gene to begin the process of mRNA synthesis that encodes for a specific protein. Low levels of mtTFA transcript and protein are associated with overall decreased mitochondrial gene transcription in cells. In contrast, expression of human mtTFA in yeast (*Saccharomyces cerevisiae*) devoid of mtTFA restores mitochondrial DNA transcription and function. Functional human mtTFA is a 25-kilodalton protein; its transcriptional activation initiates the synthesis of mitochondrial RNA by mitochondrial RNA polymerase.

The investigation of nuclear control of mitochondrial gene expression has led to the discovery of several other important transcription factors. Nuclear respiratory factor-1 (NRF-1) coordinates nuclear-encoded respiratory chain expression with mitochondrial gene transcription and replication. NRF-1 recognition sites have been found in many genes encoding respiratory functional subunits, such as rat cytochrome c oxidase subunit VIc and the bovine ATP synthase γ subunit. Therefore, NRF-1 activates mitochondrial gene expression by up-regulating mtTFA.

Another nuclear gene product, NRF-2, has also been implicated in the coordination between nuclear and mitochondrial gene expression. Although the majority of genes encoding proteins in respiratory functions have an NRF-1

recognition site, some genes (such as cytochrome c oxidase subunit IV and ATP synthase β subunit) lack an NRF-1 mitochondrial recognition site but contain a NRF-2 recognition site, indicating that these respiratory chain genes may be differentially regulated. In some genes, both NRF-1 and NRF-2 recognition sites have been identified. It is apparent that NRF-1 and NRF-2 may convey nuclear regulatory events to the mitochondria via mtTFA and coordinate the gene expression between the nuclear and mitochondrial genomes.

Peroxisomal proliferating activating receptor-γ co-activator (PGC-1) is thought to be a master regulator of mitochondrial biogenesis, and its interaction with mtTFA, NRF-1, and NRF-2 is the subject of investigation. This transcription factor has the ability to induce the production of mitochondria in brown adipose tissue. The various isoforms of PGC-1 constitute a family: PGC-1α, PGC-1β, and PGC-1-related co-activators. Both PGC-1α and PGC1-β have high expression in tissues rich in mitochondria. Unlike some other transcription factors, PGC-1α does not bind to a DNA promoter directly. Rather, it acts via a protein–protein interaction but does not have enzymatic activity. Transfection of PGC1-α into C_2C_{12} cells (i.e., introduction of PGC1-α into cells) and into myocytes results in turning on mitochondrial biogenesis. PGC1-α may act as a co-activator of NRF-1, which then is thought to bind to the promoter of mtTFA to initiate the concomitant up-regulation of both mitochondria- and nuclear-encoded proteins in a coordinated fashion. Another set of transcription factors needed to initiate mitochondrial biogenesis is the transcription specificity factors (TFB1M and TFB2M). Recognition sites are present within the promoters for NRF-1 and NRF-2 for these two transcription factors. It has also been reported that PGC1-α will up-regulate these two transcription factors. Up-regulation of mtTFA augments mitochondrial biogenesis with these other transcription factors.

folded, which greatly expands its surface area. Along with the other phospholipids common to cellular membranes, diphosphatidylglycerol or cardiolipin is found in mitochondrial membranes, particularly in the inner membrane. **Enzymes** such as monoamine oxidase, acyl coenzyme A (acyl CoA) synthetase, glycerophosphate acyltransferase, and phospholipase A_2 are associated with the outer membrane, whereas adenylyl kinase and creatine kinase are found in the intermembrane space.

The inner mitochondrial membrane is the site of oxidative phosphorylation and contains enzymes and cytochrome complexes of the **electron transport chain**. It also provides a barrier enclosing the mitochondrial matrix. The mitochondrial matrix is concentrated with enzymes, largely involved in energy nutrient oxidation, and some DNA. For instance, the enzymes associated with fatty acid oxidation as well as the Krebs cycle are found in the mitochondrial matrix. Oxidative phosphorylation produces mainly ATP, using a series of oxidative enzyme complexes known as the electron transport or respiratory chain.

BEFORE YOU GO ON . . .

1. What is the approximate composition of cell membranes in terms of percentages of proteins and phospholipids?
2. Where within the cell is it likely for carbohydrate and protein to join to become glycoproteins?
3. What are the major phospholipids in cell membranes?
4. In what cell structure would you most likely see cell detoxification occurring via the P450 pathway?
5. Name an organelle that has its own set of DNA.

The Nucleus and Genetic Aspects

The nucleus provides a storage and processing facility for DNA. It is enclosed by the porous nuclear envelope (see Figure 1.1), which is actually two separate membranes, the outer and inner. At certain regions the outer nuclear membrane connects with the membrane of the endoplasmic reticulum. This allows the space between the two nuclear membranes to be continuous with the matrix of the endoplasmic reticulum. Very large protein-associated pores penetrate the nuclear envelope, allowing molecules having a molecular weight up to 44,000 to move through the envelope with relative ease.

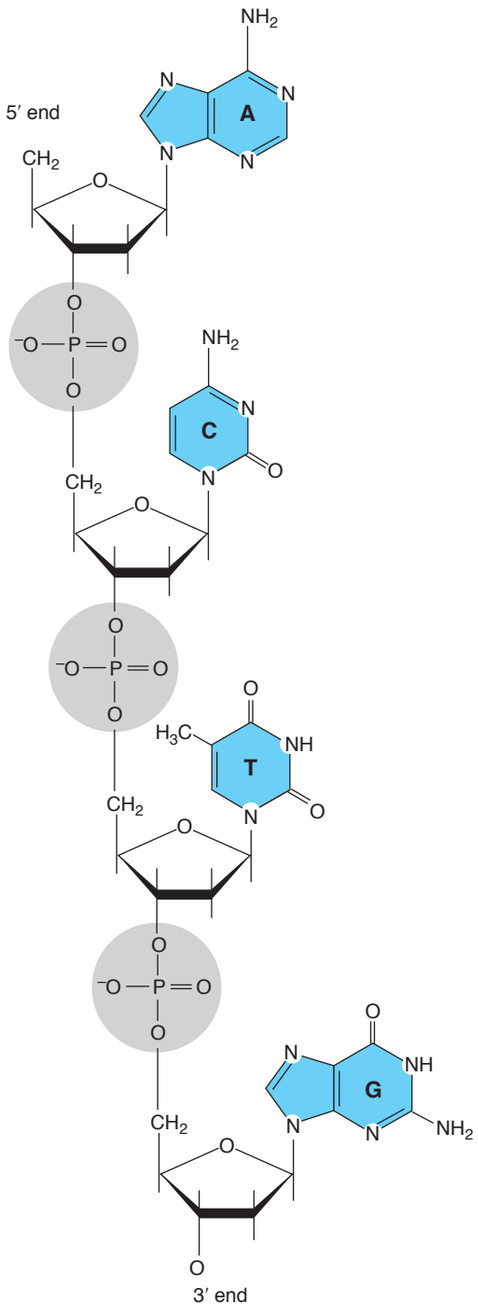


FIGURE 1.8 DNA Bases Linked by Phosphodiester Bonds, Indicated by Shaded Areas
Adapted from: Doetsch, P. W. *Encyclopedia of Life Sciences*. John Wiley & Sons, Ltd., April 2001 [doi: 10.1038/npg.els.0000557].

DNA, RNA, and Genes

By and large, the DNA contained within human cells is localized in the nucleus. Small amounts of DNA are also found in mitochondria. All mature human cells, with the exception of erythrocytes (red blood cells), contain one or more nuclei. As a rule, cells beget cells; therefore, all nucleated cells will contain the same DNA. Each DNA molecule contains a myriad of regions (**genes**) that code for proteins. Because digestion breaks down ingested food proteins into amino acids prior to absorption into the body, proteins must be constructed within cells from their building blocks—amino acids. Genes contain the instructions for the synthesis of all human proteins, including structural proteins, enzymes, contractile proteins, and protein hormones. Proteins are then involved, either directly or indirectly, in the **metabolism** of all other molecules in the human body.

DNA molecules are extremely long. It has been estimated that the longest human chromosome is over 7.2 centimeters long. Human cells contain 23 pairs of chromosomes (22 autosomal and 1 sex-linked), with the exception of sperm and eggs, which only have 1 of each of the 23 chromosomes. It has been estimated that the DNA in human chromosomes collectively codes for as many as 100,000 proteins.

Despite the fact that human DNA is a polymer consisting of billions of nucleotides linked together, there are only four nucleotide monomers (**Figure 1.8**). Adenine and guanine are purine bases, whereas thymine and cytosine are pyrimidine bases. The five-carbon carbohydrate deoxyribose is added to the bases to form adenosine (A), thymidine (T), guanosine (G), and cytosine (C). These structures, which are called nucleosides, are found in DNA in a phosphorylated form referred to as a nucleotide. DNA links of nucleotides can be written in a shorthand format, for example, ATGGATC.

DNA exists in human cells as double-stranded chains arranged in an antiparallel manner. That is, one DNA polymer runs in a 3′ to 5′ direction whereas the complementary stand runs in a 5′ to 3′ orientation. The strands are held together by complementary base pairing, whereby adenosine on one strand hydrogen-bonds with thymidine on the other chain, and guanine base-pairs with cytosine (**Figure 1.9**). The average length of human genes is about 20,000 base pairs.

Whereas DNA in the nucleus is substantial in quantity and strongly associated with histone proteins to form complex chromosomal structures, the DNA in mitochondria contains fewer than 17,000 base pairs and contains a very limited number of coding regions. Mitochondrial DNA contains genes for 13 of the 67 or so protein subunits of the respiratory chain as well as for **ribosomal RNA** (**rRNA**) and **transfer RNA** (**tRNA**).

The processes of protein synthesis have to overcome a few obstacles. First, genes coding for proteins are located

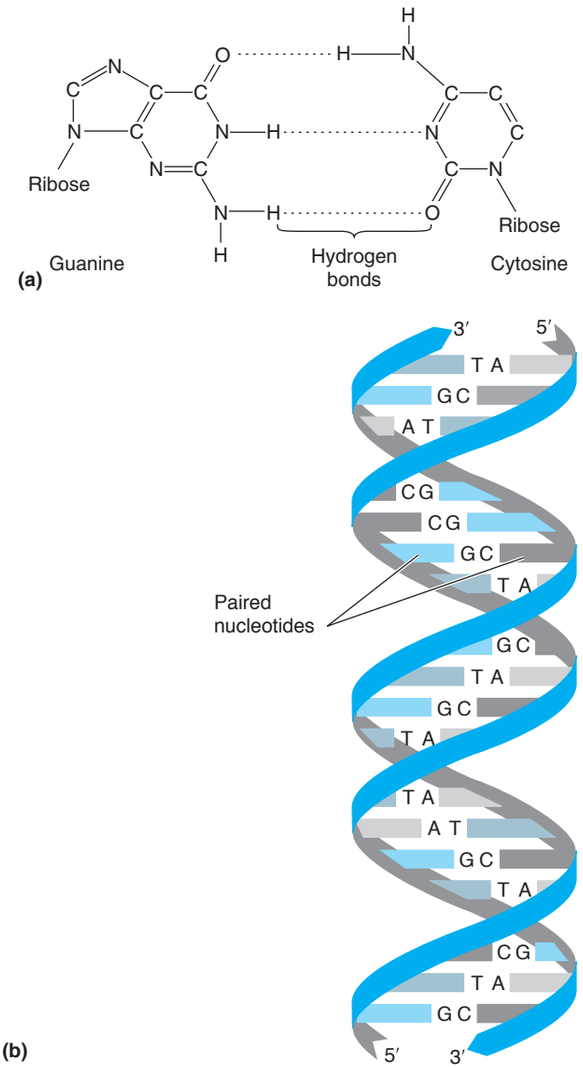


FIGURE 1.9 Hydrogen Bonding Between Complementary Nucleotide Bases. The hydrogen-bond link between adenine and thymine (a), and hydrogen bonding between the double helical DNA stands (b).

primarily within the nucleus. Meanwhile, ribosomal complexes, which are the apparatuses of protein synthesis, exist either within the cytosol or studding the endoplasmic reticulum. Thus, the information inherent to DNA must be delivered from one location to another. This obstacle is overcome by **messenger RNA** (**mRNA**). Second, the amino acids necessary to synthesize proteins must be made available at the site of protein synthesis. This obstacle is overcome by tRNA. Amino acids are delivered to ribosomal complexes by tRNA and correctly

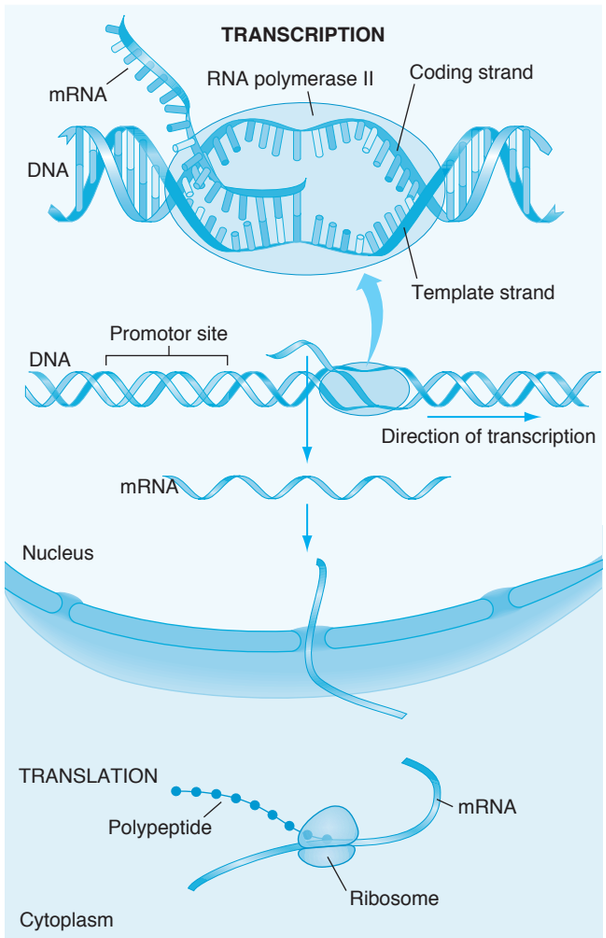


FIGURE 1.10 Protein Synthesis

oriented to allow their incorporation into growing protein chains (**Figure 1.10**).

Protein synthesis begins with **transcription**, the process of producing a strand of mRNA that is complementary to the DNA gene being expressed. First the double-stranded DNA is temporarily opened at the site of the gene, and then ribonucleotides are sequentially base-paired to the DNA template. The process is catalyzed by RNA polymerase II and influenced and regulated by promoter and enhancer sequences of DNA occurring either prior to or after the coding region. The formation of the DNA–RNA complementary base-pairing is the same as for DNA–DNA base-pairing, with one exception: the pyrimidine base uracil (U) substitutes for thymine in base-pairing with adenine. In addition to the substitution of a uracil base for thymine, the nucleotides contain **ribose** instead of deoxyribose.

Base-Pairing of Nucleic Acid Bases

DNA–DNA	DNA–RNA
A–T	A–U
C–G	C–G

The initial RNA strand created during transcription, called **heterogeneous nuclear RNA** (**hnRNA**), is relatively large and generally unusable in this state. Therefore, the newly created hnRNA strand must undergo **post-transcriptional modification**, or change in the original molecule produced following transcription. Segments of the hnRNA strand that do not code for the final protein must be removed, and the remaining segments that do code for the final protein must be joined together. This process is called **splicing**; the removed segments are referred to as **introns**, and the remaining segments are **exons**. Furthermore, the RNA strand is modified at both ends.

The ribosomal complexes providing the site of protein synthesis must be constructed from RNA subunits. DNA contains specific regions that, when transcribed, produce RNA strands that are not used in instructing protein amino acid sequencing but rather are used to construct ribosomal complexes. The enzyme RNA polymerase I transcribes the rRNA 45S precursor, which undergoes a number of cleavages and ultimately produces 18S and 28S rRNA. The latter rRNA is hydrogen-bonded to a 5.8S rRNA molecule. Finally, a 5S rRNA is produced by RNA polymerase III. The 18S rRNA complexes with proteins to form the 40S ribosomal subunit, whereas the 28S, 5.8S, and 5S rRNA complex with proteins to form the 60S ribosomal subunit. The 40S and the 60S ribosomal subunits migrate through the nuclear pores and ultimately condense to form the 80S ribosome, which, once situated, becomes a site of protein synthesis.

At least three types of RNA are involved in silencing gene expression; they are commonly referred to as **RNA interference** (**RNAi**). The first one is called **micro RNA** (**miRNA**), and it appears to control translation events in animal cells. miRNA is composed of only a few nucleotide base pairs, approximately 22, and is encoded by the cell's genomic DNA. The human genome encodes more than 1,000 types of miRNA. miRNA is mostly involved in suppressing translation by binding to the complementary sequences of mRNA at the 3′ untranslated region (UTR). miRNA sequences are not 100% complementary to the mRNA and may differ by at least one base pair. This difference may block translation of a peptide or protein. Regardless, these processes are sometimes referred to as gene silencing. Approximately 60% of human genes may be targeted by miRNA, and miRNA may be involved in hundreds of biological processes. Because miRNA is also found in mitochondria, it may also affect the ability of mitochondria to multiply and mature.

The second type of RNAi is referred to as **small interfering RNA** (**siRNA**)**.** This type of RNA is very similar to miRNA except that (1) it is synthetic and used for biological experimentation to silence genes and (2) it is an exact match to the mRNA. Because of the 100% match, when the siRNA pairs with the complementary mRNA, the complex is destroyed, which is different from miRNA, which blocks protein translation.

Finally, there is **small hairpin RNA** (**shRNA**), which functions like miRNA but is used more as an experimental agent. shRNA silences genes by introducing them into a cell that is fused to a vector, such as a plasmid or a virus. This shRNA introduction can then lead either to RNA degradation, in the case of a perfect base-pair match, or a block in translation, in the case of an imperfect base-pair match.

Protein Synthesis

For proteins to be constructed, the genetic nucleotide language must be translated into amino acid chains. This fact led to the coining of the term **translation**. Amino acids are specifically linked together as dictated by the sequencing of RNA in the finalized version of mRNA. Messenger RNA contains a series of triplets of bases coding for a given amino acid. These coding triplets, or codons, are the complementary base triplets originally transcribed in DNA (**Table 1.5**). RNA codons in mRNA either indicate a specific amino acid or signal for either the initiation or termination of the synthesis of a protein. Certain amino acids have more than one RNA triplet; for example, alanine has four codons, and arginine has six. Other amino acids only have a single codon; for example, methionine and tryptophan both have only one codon apiece. Codons are nearly universal, meaning that they will code for the same amino acids in most species; however, some differences have been found in codons translated in mitochondria.

Transfer RNA constitutes small cytosolic RNA molecules of about 80 nucleotides in length. Transfer RNA attaches to specific amino acids and delivers them to ribosomal complexes. Transfer RNA is then able to recognize when to include its amino acid into a growing protein chain by codon–anticodon recognition. Each tRNA contains a triplet of bases that will interact with its complementary codon on the mRNA strand being translated. This allows the sequencing of amino acids into growing protein chains to be a very accurate process.

Proteins that are synthesized on ribosomal complexes studding the endoplasmic reticulum thread into the

TABLE 1.5 Genetic Code

First Base	Second Base				Third Base
(5′)	*U*	*C*	*A*	*G*	*(3′)*
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Term[a]	Term	A
	Leu	Ser	Term	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

[a]Term indicates a stop or termination codon.

endoplasmic reticulum matrix. As mentioned previously, these proteins are, by and large, modified by the addition of carbohydrate moieties to form glycoproteins. In contrast, proteins formed in association with cytosolic ribosomal complexes mostly remain as free proteins. Again, the free proteins formed in the cytosol remain mostly within the cell, whereas most of the protein formed in association with the endoplasmic reticulum is destined for exocytosis from the cells or to become part of cell membranes.

From an energy standpoint, protein synthesis is a very ATP-expensive operation. To begin with, amino acids must be activated before they can attach to their corresponding tRNA. Thus, if a synthesized protein contains 500 amino acids, then 500 ATP molecules must be used simply in forming amino acid–tRNA associations. Furthermore, the initiation of translation, as well as protein elongation, requires even more energy. A portion of the energy demand is provided by the hydrolysis of guanosine triphosphate (GTP). It is estimated that every amino acid–amino acid linkage in a protein requires the energy contribution made by the hydrolysis of four high-energy bonds, provided by ATP and GTP.

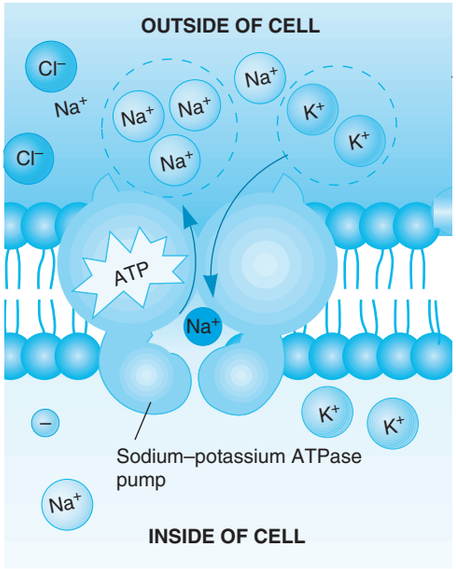


FIGURE 1.11 Sodium–Potassium ATPase Pump. Adenosine triphosphate (ATP) is hydrolyzed to provide the energy necessary to concomitantly pump sodium and potassium across the plasma membrane against their concentration gradient. For instance, sodium is pumped to the outside of the cell and potassium is pumped to the inside of the cell.

Electron Transport Chain and Oxidative Phosphorylation

Perhaps the most important function of any cell in the human body is the formation of ATP. ATP is then used by cells to promote three major categories of function: membrane transport, synthesis of molecules, and mechanical work. Substances either directly or indirectly transported by active, or ATP-requiring, processes include sodium, potassium, chloride, urate, and hydrogen ions as well as other ions and organic substances (**Figure 1.11**). The cost of active transportation can be extremely heavy in some cells. For example, tubular cells in the kidneys contribute as much as 80% of their ATP expenditure to active transport. The synthesis of chemical compounds in cells, such as proteins, purines, pyrimidines, cholesterol, phospholipids, and a whole host of other compounds, is also extremely energy costly. Some cells may dedicate as much as 75% of their produced ATP to synthetic processes. With regard to mechanical work performed by cells, muscle fiber contraction accounts for most of the ATP used for these specialized processes. The balance comes mostly from the minimal contribution of ameboid and ciliary motion performed by certain cells.

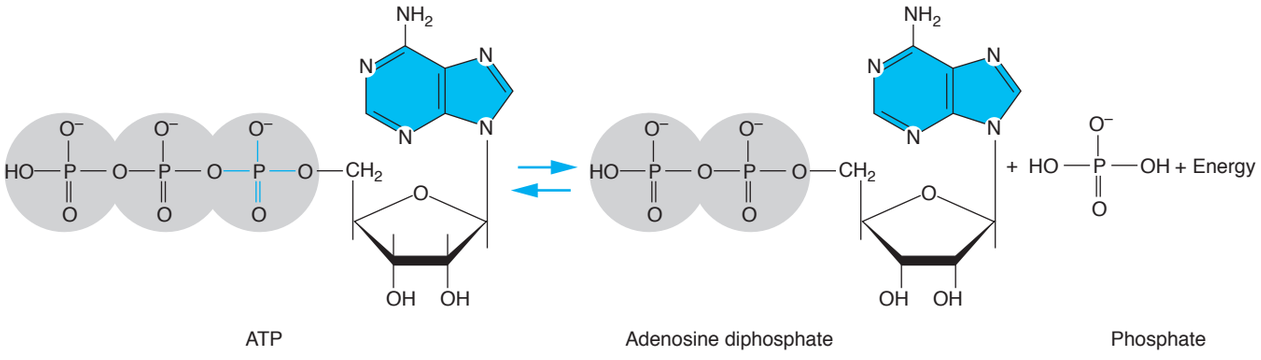


FIGURE 1.12 Adenosine Triphosphate (ATP). ATP is the primary high-energy molecule produced in human cells. Bonds between the phosphate groups are hydrolyzed to liberate energy, which is applied to cellular processes.

ATP is constantly consumed and regenerated in human cells. The structure of ATP, which is depicted in **Figure 1.12**, reveals an adenine base linked to ribose, which itself has a tail of three phosphates linked in series by anhydride bonds. The free energy derived from ATP comes from the hydrolytic splitting of anhydride bonds. These bonds thus became known as **high-energy bonds**. When ATP is hydrolyzed to produce ADP, the change in standard Gibbs free energy ($\Delta G^{\circ\prime}$) equals –7.3 **kilocalories**/mole. The free energy released when ATP is hydrolyzed is used to drive reactions that require energy. Generally, adenosine diphosphate (ADP) is formed along with inorganic phosphate (P_i). ADP can be broken down to adenosine monophosphate (AMP) and pyrophosphate (PPi), which releases −3.4 kilocalories/mole. Furthermore, ATP can transfer a phosphate group to compounds such as glucose. ATP, ADP, and AMP are interconvertible by the adenylate kinase reaction:

$$\text{ATP} + \text{AMP} \leftrightarrow 2\ \text{ADP}$$

Carbohydrates, amino acids, triglycerides, ethanol, and their intermediates, derived directly from the diet or mobilized from cellular stores, provide the substrates for ATP formation. As discussed in greater detail later, these fuel molecules must engage in various chemical reaction series or pathways in order for their inherent energy to be used in the formation of ATP. The utilization of carbohydrate begins with a series of chemical reactions occurring in the cytosol known as **glycolysis**. Glycolysis generates a net production of two ATP molecules by substrate-level phosphorylation, an anaerobic process. Glycolysis generates pyruvate molecules, which can enter mitochondria and be converted to the activated two-carbon residue acetyl coenzyme A (CoA). Likewise, the breakdown of fatty acids, some amino acids, and ethanol also results in the production of acetyl CoA.

Mitochondrial acetyl CoA condenses with oxaloacetate to form citrate, which then enters the Krebs cycle (**Figure 1.13**). The Krebs cycle, also known as the citric acid cycle and the tricarboxylic acid (TCA) cycle, is a series of seven main chemical reactions in which the final reaction regenerates oxaloacetate. Therefore, this pathway is considered cyclic. The net result of these reactions is the production of reduced cofactors that will then transfer the electrons to the electron transport chain. NADH and $FADH_2$ are the reduced forms of NAD^+ (oxidized nicotinamide adenine dinucleotide) and FAD (flavin adenine dinucleotide), respectively. Reactions in the Krebs cycle produce three NADH and one $FADH_2$. **Fatty acid oxidation** (β-oxidation) also creates NADH and $FADH_2$; how many of the reduced cofactors are produced depends on the length of a particular fatty acid. Furthermore, NADH is also produced in the conversion of pyruvate to acetyl CoA in the mitochondria, as well as during glycolysis in the cytosol.

Carbon dioxide is produced in the conversion of pyruvate to acetyl CoA and in two reactions in the Krebs cycle. These reactions are the primary producers of this metabolic waste molecule in cells. GTP is also generated by a reaction in the Krebs cycle and functions to drive certain biochemical reactions, such as translation.

As mentioned earlier, ATP is generated **anaerobically** in one chemical reaction of glycolysis. This is an important source of ATP for all cells and is the sole source of ATP for erythrocytes (red blood cells), which lack mitochondria. However, most of the ATP generated within cells occurs via oxidative phosphorylation by the electron transport chain. Oxygen is required for operation of the

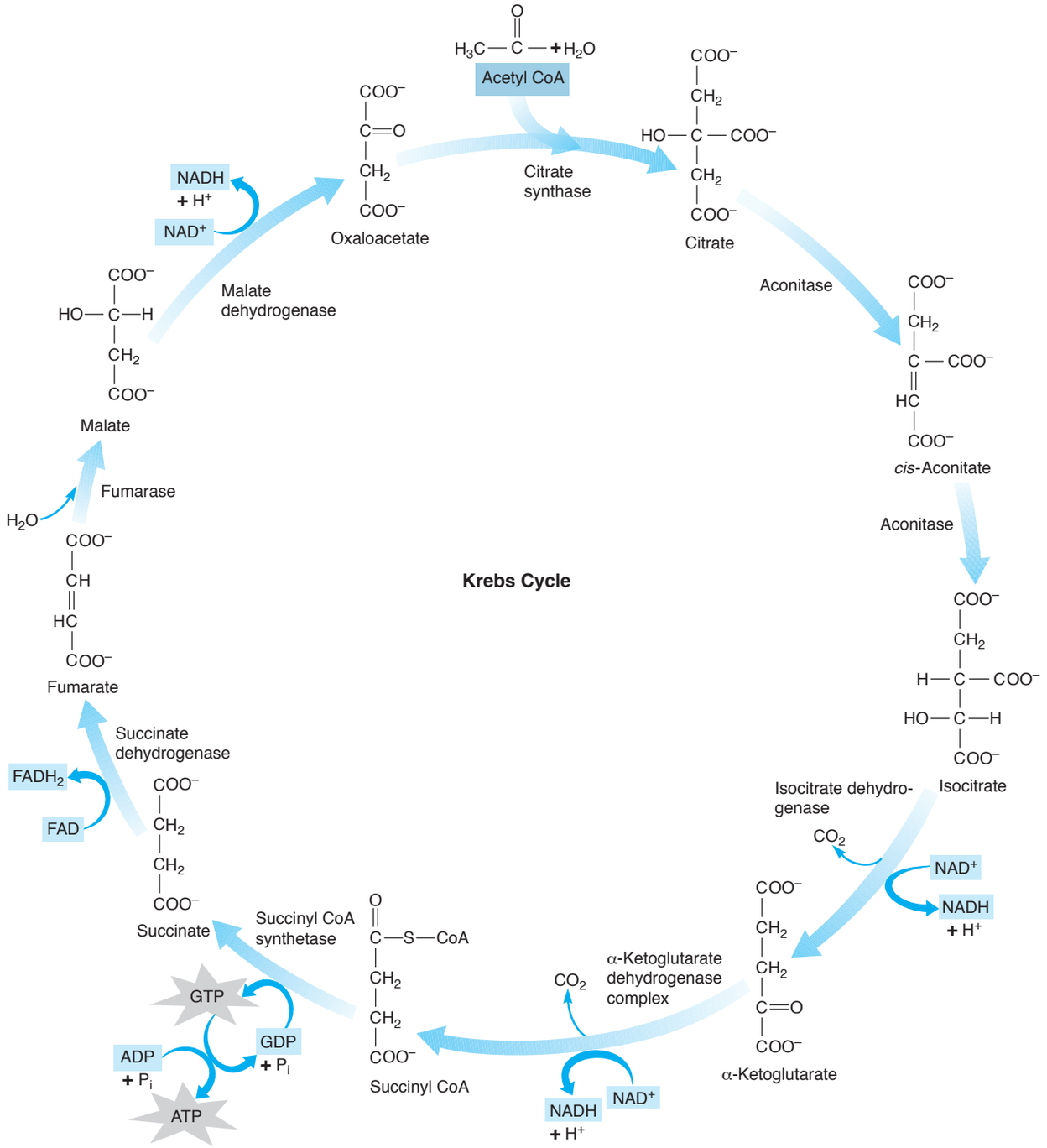


FIGURE 1.13 **The Krebs (Citric Acid) Cycle**

electron transport chain as the final acceptor of electrons. Without the availability of oxygen, the flow of electrons through the electron transport chain is halted and mitochondrial ATP generation ceases (**Figure 1.14**).

The electron transport chain is a series of protein-based complexes stitched into the mitochondrial inner membrane. The inner membrane is highly folded, which increases its surface area and thus the number of electron

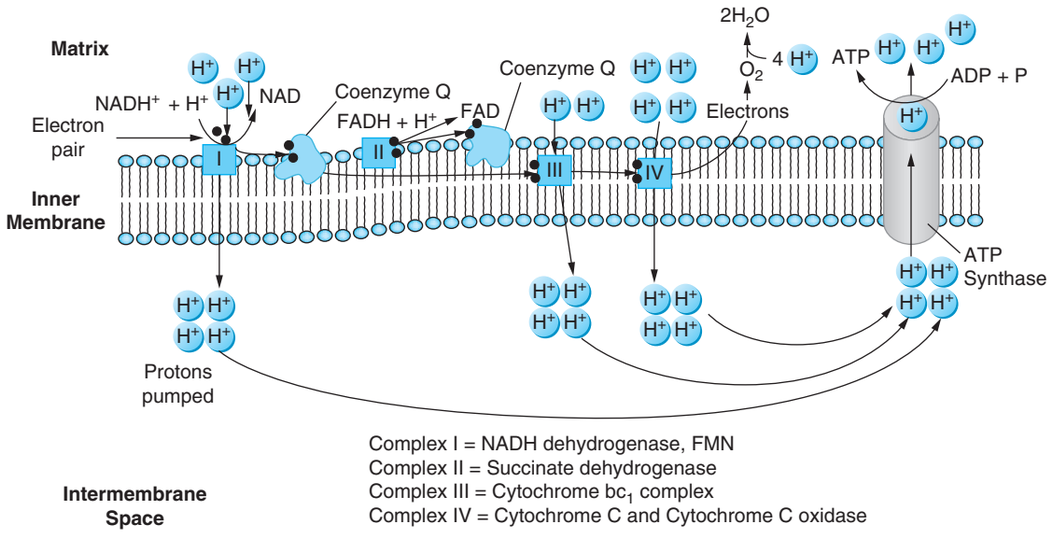


FIGURE 1.14 Electron Transport Chain. Note that O_2 is the final electron acceptor.

transport chains per mitochondrion. The folds are known as cristae. Mitochondria of certain cells, such as cardiac muscle cells, are densely packed with cristae (**Figure 1.15**).

The reduced cofactors NADH and $FADH_2$ transfer electrons to the electron transport chain. NADH is viewed as free-floating within the mitochondrial matrix as well as the cytosol. Thus, when NAD^+ becomes reduced to NADH it can diffuse to electron transport chains. This certainly seems true of NADH generated within the mitochondria. However, NADH produced in the cytosol probably must rely on an electron-translocation system for its electrons to reach the electron transport chain. Conversely, FAD is bound tightly to enzymes in the mitochondrial inner membrane. Thus, FAD reduced to $FADH_2$ will not need to endure diffusion and is in theory immediately available to the electron transport chain.

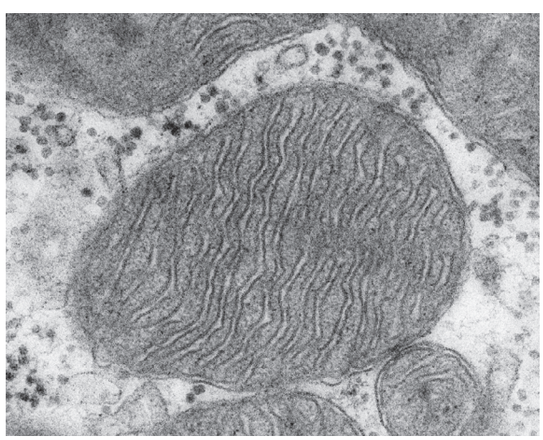


FIGURE 1.15 Electron Micrograph of Cardiac Myocyte Mitochondria (25,000×). Note the densely packed inner membrane, or cristae.

Electrons move forward through the electron transport chain toward O_2 because of the large $\Delta G^{\circ\prime}$ gradient. The transfer of electrons from NADH to O_2 occurs in three stages, each of which is associated with the production of one ATP molecule. Meanwhile, the transfer of electrons from $FADH_2$ to O_2 occurs in two principal steps, both of which are associated with the production of one ATP molecule. Therefore, three ATP molecules will be created for each NADH oxidized, and two ATP molecules will be created for each oxidized $FADH_2$.

Electrons are passed from NADH to flavin mononucleotide (FMN) as catalyzed by NADH dehydrogenase (Complex I). FMN then passes the electrons through series of iron–sulfur (Fe-S) complexes to coenzyme Q (CoQ). Coenzyme Q accepts the electrons one at a time, first forming semiquinone and then ubiquinol. The energy liberated by the transfer of electrons at this point is adequate to pump protons to the cytosolic side of the mitochondrial inner membrane. The pumping of electrons at this and other points of the electron transport chain establishes a chemoelectrical potential or proton-motive force. Because the mitochondrial inner membrane is generally impermeable to proton diffusion, movement of protons back into the matrix occurs

through highly specialized ATP-synthase complexes (F_0-F_1/ATPase). F_0 proteins form a physical channel allowing proton passage through the membrane and are also connected to the F_1 (ATP-synthesizing head) proteins. This is the site of ATP formation. $FADH_2$ also passes its electrons to Complex II and then coenzyme Q; however, because the FMN stage was bypassed, there is no associated pumping of a proton across the mitochondrial inner membrane.

Electrons are transferred from coenzyme Q to cytochrome b and c_1 (Complex III) and then to cytochrome c via the actions of cytochrome reductase. These cytochromes, along with others in the electron transport chain, consist of an iron-containing heme prosthetic group associated with a protein. Enough energy is liberated in the transfer of electrons from coenzyme Q to cytochrome c to pump a proton across the inner membrane.

Cytochrome c transfers electrons to the cytochrome aa_3 complex (Complex IV), which then transfers the electrons to molecular oxygen, creating water. Cytochrome c oxidase is the enzyme involved with the transfer of electrons to oxygen, and again the energy liberated is significant enough to pump another proton across the mitochondrial inner membrane.

BEFORE YOU GO ON . . .

1. What are gene-silencing RNAs, and why are they significant?
2. What is meant by post-transcriptional modification?
3. State what purine and pyrimidines are and which base pairs are complementary with one another.
4. What is the major purpose of NADH and $FADH_2$?
5. What is the chemoelectrical force in regard to electron transport?

Cellular Protein Functions

Thus far we have learned how a cell makes proteins. As you can imagine, there are thousands of proteins serving a wide variety of functions. Proteins are required for organelle and cell membrane structure, are components of cell receptors, and play a critical role in cell signaling (e.g., protein kinases). Proteins may act as chaperones for other compounds or minerals to other parts of the cell. Proteins are also components of ion channels and, equally as important, make up enzymes to facilitate cellular biochemical reactions. Let's consider each of these protein functions separately.

Organelle and Cell Membrane Structure and Cell Receptors

Organelle and cell membranes are composed of a biphospholipid layer in which proteins are embedded. Many of the proteins embedded in cell membranes may be ion channels or transport proteins. Proteins often exist on cell membranes, where they may crisscross the cell membranes several times. For example, the 5′ (carboxyl) end and 3′ (amino) end of a protein may be at the intracellular or extracellular level (**Figure 1.16**). Often these transport proteins bind to a substrate (e.g., glucose) and the transport protein changes conformation to bring a substrate into the cell (**Figure 1.17**) or export material out of a cell. Zinc transporter proteins are a good example of this mechanism. In many cases, such as the sodium–potassium (Na^+-K^+) ATPase pump, energy in the form of ATP is needed to extrude sodium from the inside of the cell to the exterior and pump potassium into the cell.

Enzymes

All enzymes are composed of proteins. Some of these enzymes have carbohydrate components and even minerals to help them function at an active site. You may remember from biochemistry that an active site is where an enzyme and substrate bind and where the chemical reaction occurs, which normally requires energy. Enzymes facilitate metabolic reactions in a cell and allow the cell to use less energy (normally ATP) to cause a reaction to occur. The energy

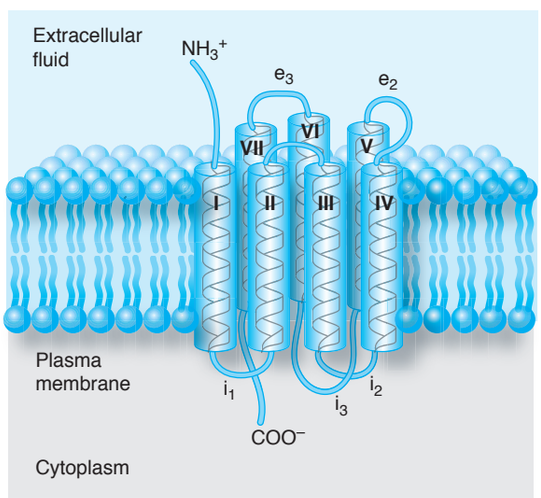


FIGURE 1.16 Structure of a Transmembrane Protein Receptor
Adapted from: Bockaert, J. *Encyclopedia of Life Sciences*. John Wiley & Sons, Ltd., January 2006. [doi: 10.1038/npg.els.0000118].

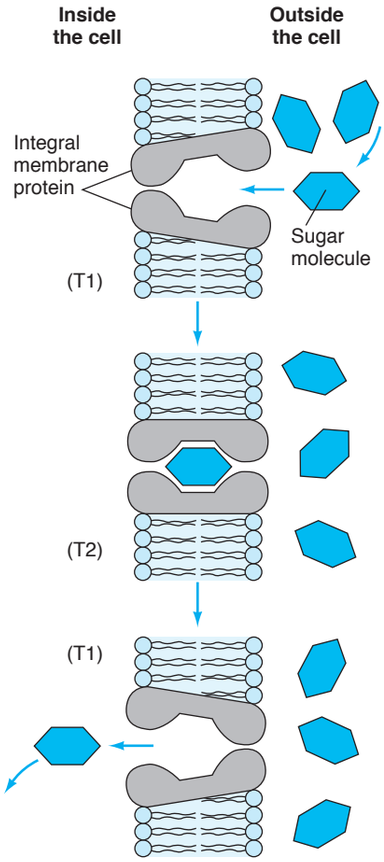


FIGURE 1.17 Conformation Change of Some Transmembrane Receptors When Importing or Exporting a Substance. In this case, note the change in the transport protein for a sugar molecule as it goes from the outside to the inside of the cell. T1 is the transport protein without a sugar molecule, and T2 is the same protein that has a conformational change when binding to a sugar molecule.

needed to cause a biochemical reaction to occur is often called the energy of activation. An enzyme lowers the energy of activation, which in essence means that the cell requires less energy for a reaction to occur. ATP is normally a source of energy involved in enzymatic reactions. For example, consider the following reactions. Glucose is converted to **glucose-6-phosphate** in the presence of ATP; the enzyme glucokinase (sometimes referred to as hexokinase) is essential for this reaction. In contrast, the conversion of malate into oxaloacetate does not require ATP, but does require the enzyme malate dehydrogenase.

Cell Signaling

Phosphorylation and dephosphorylation of proteins may activate or deactivate proteins involved with enzymatic reactions and pathways. Certain proteins involved with hormonal regulations have a protein receptor for the hormone. Cyclic AMP, or cAMP (3′,5′-cyclic adenosine monophosphate), is formed from ATP. cAMP is often called a second messenger because it acts as a messenger for hormones. Inositol-P_3 is another second messenger. The hormone receptor reacts with another intracellular protein, most likely a G protein (**Figure 1.18**). G proteins are an integral part of protein signaling to generate a second messenger.

Cell signaling consists of a series of biochemical reactions from the cell surface receptor to convey the message to a DNA promoter to exert the desired effect, for example, transcription of mRNA. Not all signaling has to be genetic; some may simply involve phosphorylation and dephosphorylation, as described earlier. The impact of a G protein is not a simple one-step reaction of turning a gene off or on, but rather is a series of coordinated reactions that act as a cascade leading to a final outcome. A hormone reacting with its receptor may activate a G protein in order to activate adenylate cyclase to produce cAMP, which, in turn, can cause many metabolic reactions.

Transport

As alluded to previously, proteins are vital in the transport of many nutrients within the **enterocyte** and all living cells. Proteins act as conduits to bring compounds into a cell either by passive (or **facilitated**) **diffusion**, in which no energy is needed to pass down a concentration gradient, or by **active transport**, for which energy is required. The uptake of amino acids and monosaccharides occurs against a concentration gradient and requires ATP; thus, it is an example of active transport. We mentioned active transport earlier when discussing Na^+-Ka^+ transport, which is really a co-transport mechanism requiring ATP. (**Co-transport** means one mineral or compound is coming in and one is going out at the same time by the same transport protein.) Carrier-mediated transport is usually saturable, meaning that at some point a concentration of compounds is reached such that further uptake is not possible because all the binding sites of the transporter have been occupied by the solute being transported.

Hormones

There are two ways in which one region of the human body can communicate with another. The first is by way of nerve impulses, and the second is by way of hormones. Hormones are synthesized by endocrine glands of various organs, including the pituitary gland, parathyroid

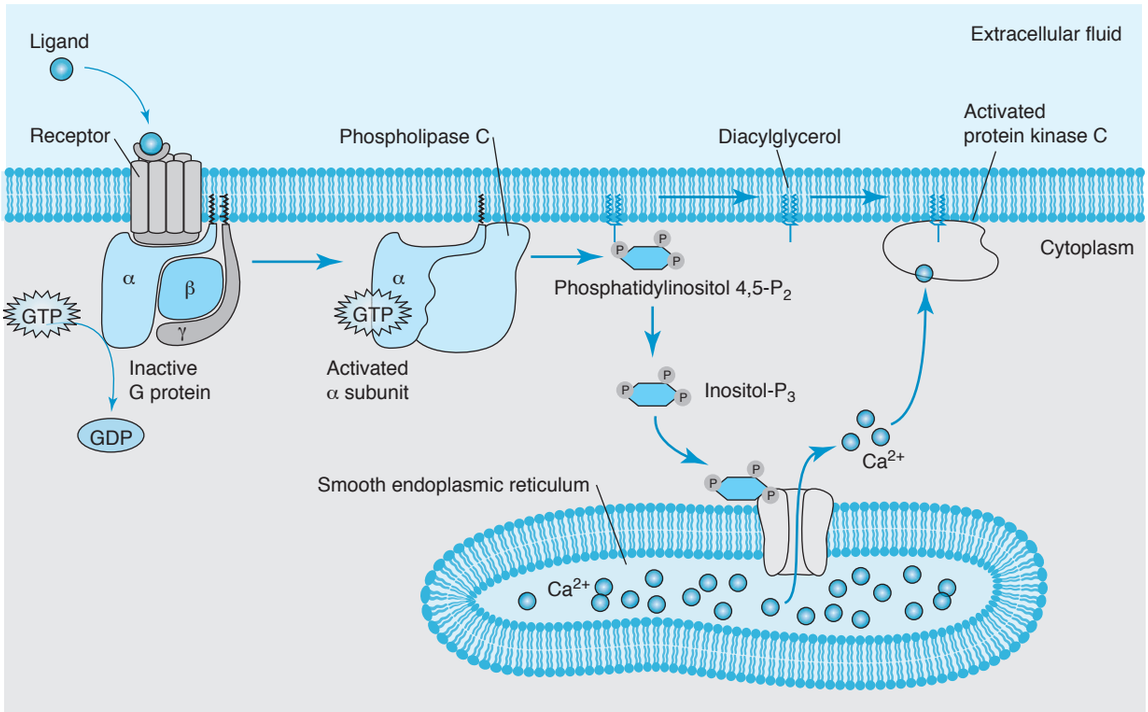


FIGURE 1.18 A Hormone (ligand) Interacting with a Receptor and a G Protein to Generate a Second Messenger, in This Case Inositol-P_3
Adapted from an illustration by George M. Helmkamp, Jr., School of Medicine, University of Kansas.

gland, thyroid gland, hypothalamus, pancreas, stomach, small intestine, adrenal glands, placenta, and gonads (ovaries and testicles) (**Figure 1.19**). They are large protein and protein-based (i.e., glycoproteins), amino acid–based, or cholesterol-derived steroid molecules. Examples of protein hormones include insulin, growth hormone, glucagon, and antidiuretic hormone. Examples of hormones made from the amino acid tyrosine are epinephrine

SPECIAL FEATURE 1.3

Peroxisomes: The Lost Organelle

Many biology texts only mention peroxisomes in passing and do not focus on their function. However, they play an important role in human health and disease and are metabolically active structures in cells. Peroxisomes contain oxidative enzymes, such as D-amino acid oxidase, urate oxidase, and catalase. In fact, there may be as many as 50 different enzymes in peroxisomes. Under a microscope, peroxisomes have a crystalline structure inside a sac that contains amorphous gray material. They are self-replicating, much like mitochondria, and may look like granules.

A major function of peroxisomes is to eliminate toxic substances from the body, including hydrogen peroxide. This is notable because peroxisomes can create hydrogen peroxide but also contain the catalase to break it down. Peroxisomes are numerous in liver cells, which is to be expected because toxic by-products tend to accumulate there.

From a nutrition perspective, a major function of peroxisomes is the breakdown of fatty acids. In fact, this breakdown process is what generates hydrogen peroxide. Usually, peroxisomes are the cell organelles in which fatty acids longer than 20 carbons (known as very long chain fatty acids) undergo beta oxidation, followed by transfer to the mitochondria for the remaining oxidation. The number of peroxisomes is under genetic control that is mediated through a nuclear receptor called peroxisome proliferator-activated receptor alpha (PPARα). Clinically, peroxisomes have been known to possess inborn errors of metabolism whereby enzymes needed for the breakdown of fatty acids are deficient or lacking. Such diseases can lead to lipid buildup in the liver and have serious medical outcomes.

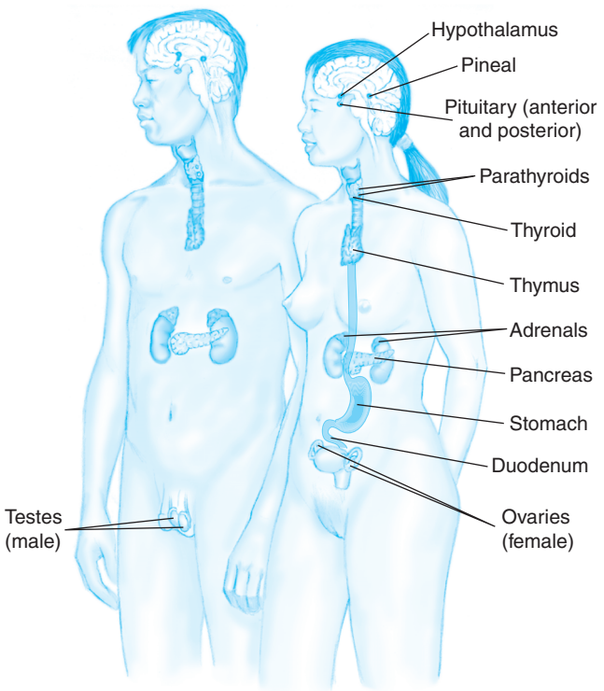


FIGURE 1.19 **Endocrine Organs**

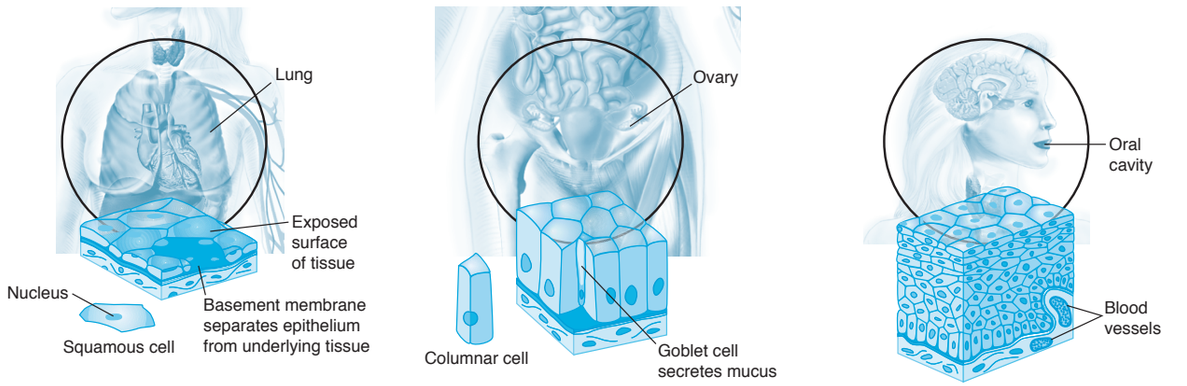
(adrenalin) and the thyroid hormones (triiodothyronine and thyroxine). Steroid hormones are made from cholesterol and include testosterone, estrogens, cortisol, progesterone, and aldosterone.

Hormones are released into circulation and interact with specific receptor complexes on one or more tissues. Only those cells that have a specific receptor for a given hormone will respond to that hormone. Some cell receptors are located on the plasma membrane and are typically part of a larger complex that has an associated intracellular event upon binding. For instance, the binding of the pancreatic hormone glucagon to glucagon receptors on tissue such as the liver results in an increase in cytosolic cAMP levels. As noted earlier, because cAMP is responsible for initiating the glucagon-intended cellular events, cAMP is a second messenger. There are other second messengers as well, such as Ca^{2+}, cyclic guanosine monophosphate (cGMP), inositol triphosphate, and diacylglycerol. Other hormones, such as thyroid hormones and steroid-based hormones, have nuclear receptors. These hormones exert their activity by influencing gene expression (**Table 1.6**).

Some hormones may have receptors on cells of only one kind of tissue, whereas others may have receptors on cells of several different types of tissues. For example, the

TABLE 1.6 Select Hormones Related to Nutrition and Metabolism and Their General Function

Source	Hormone	Principal Activity
Pituitary gland	Growth hormone	Increases growth of most tissue by increasing protein synthesis and increasing fat utilization for energy
	Prolactin	Increases mammary milk formation during lactation
	Antidiuretic hormone	Decreases H_2O loss by kidneys by increasing H_2O reabsorption in nephrons
Thyroid gland	Thyroid hormone	Increases rate of metabolism
	Calcitonin	Decreases blood calcium levels by increasing kidney loss and decreasing digestive absorption of calcium
Parathyroid gland	Parathyroid	Increases blood calcium levels by increasing bone resorption
Adrenal glands	Aldosterone	Increases sodium reabsorption in kidneys
	Cortisol	Increases glucose release into blood from liver by increasing gluconeogenesis
		Increases protein catabolism, which increases amino acid availability for gluconeogenesis
	Epinephrine (adrenalin)	Increases heart rate and stroke volume, increasing glucose release into blood from liver
		Increases glycogen breakdown in liver and muscle
		Increases fat mobilization from fat cells
Pancreas	Insulin	Increases glucose uptake by fat cells and skeletal muscle
		Increases processing of fat and glycogen production and storage
		Increases amino acid uptake and protein production
	Glucagon	Increases fat release from fat cells
		Increases liver glycogen breakdown
		Increases glucose production in liver



(a) Simple squamous epithelium
Lining of blood vessels, air sacs of lungs, kidney tubules, and lining of body cavities

(b) Columnar epithelium
Lining of the digestive tract and upper part of the respiratory tracts, auditory and uterine tubes

(c) Stratified squamous epithelium
Skin, mouth, and throat lining; vaginal lining; anal lining; and cornea

FIGURE 1.20 Epithelia. Different types of epithelia include simple squamous (a), columnar (b), and stratified squamous (c).

hormone prolactin stimulates milk production in female breasts. Therefore, the cells associated with the milk-producing mammary glands have receptors for prolactin, whereas cells of most other kinds of tissue do not have prolactin receptors. In contrast, growth hormone receptors are found on cells of many kinds of tissue in the body.

Steroid hormones have a much different way of exerting an influence. A steroid receptor binds in the cytoplasm or nucleus to a receptor that then binds to the promoters of a gene or DNA. The influence of most of these complexes is to turn a gene on, or initiate the transcription process.

BEFORE YOU GO ON . . .

1. What does an enzyme essentially do to facilitate a biochemical reaction in a cell?
2. What are some of the functions proteins play within a cell membrane?
3. How do protein hormones differ from steroid hormones in exerting their effect?
4. Name a key protein involved with cell signaling.
5. What is facilitative diffusion?

Tissue

Similar cells performing similar or supportive tasks constitute tissue. All of the 200 or so cell types in the human body are generally classified as belonging to four basic kinds of tissue. Many biochemistry students study biochemical pathways without an appreciation that not all of these pathways occur to the same degree in each cell or all tissues.

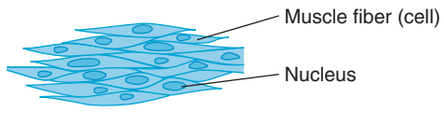
Epithelial cells line surfaces such as blood vessels; reproductive, digestive, and urinary tracts; ducts; and skin. They are subclassified into four types of epithelial cells: simple squamous, stratified squamous, columnar (**Figure 1.20**), and cuboidal. **Muscle** tissue is primarily composed of contractile muscle cells (myocytes) and includes skeletal, cardiac, and smooth muscle cell types (**Figure 1.21**). Although the general purpose of muscle tissue is to contract, the different types of muscle have structural and physiologic differences. **Nervous tissue**, such as in the central and autonomic nervous systems and other nerves, allows for communication and sensory perception. Finally, **connective tissue** is the most abundant, widely distributed, and varied tissue type. It exists as a thin mesh or webbing that helps hold tissue and organs together as well as providing strong fibers for bones, cartilage, and tendons. Blood is considered a form of connective tissue.

Organ Systems

Organs are structures that are made up of two or more kinds of tissue. The contributing tissues are organized in such a way that they can perform more functions than the single tissue alone. Organ systems are groups of organs arranged in a manner such that they can perform a function more complex than any of the organs independently. **Table 1.7** lists the 10 organ systems in the human body and their component organs.

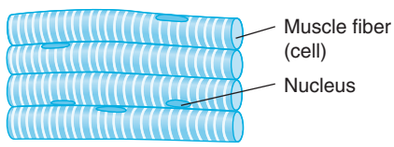
Smooth muscle
Walls of hollow organs, pupil of eye, skin (attached to hair), and glands

DESCRIPTION Tissue is not striated; spindle-shaped cells have a single, centrally located nucleus
FUNCTION Regulation of size of organs, forcing of fluid through tubes, control of amount of light entering eye, production of "gooseflesh" in skin; under involuntary control



Skeletal muscle
Attachment to bone

DESCRIPTION Tissue is striated; cells are large, long, and cylindrical with several nuclei
FUNCTION Movement of the body, under voluntary control



Cardiac muscle
Heart

DESCRIPTION Tissue is striated; cells are cylindrical and branching with a single centrally located nucleus
FUNCTION Pumping of blood, under involuntary control

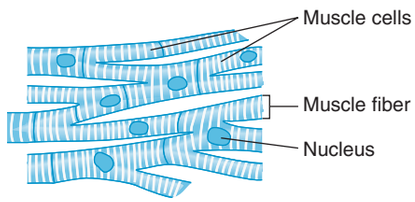


FIGURE 1.21 Muscle Cell Types

Bone and the Skeleton

The human **skeleton** is a combination of 206 separate bones as well as supporting ligaments and cartilage. The bones of the skeleton are attached to muscles, which allows for locomotion. Bones are also used for protection. The skull and the vertebrae enclose the brain and spinal cord, respectively, thereby protecting the central nervous system. Twelve pairs of ribs extend from the vertebrae and protect the organs of the chest. Bone also serves as a storage site for several minerals, such as calcium and phosphorus, and is the site of formation for red blood cells (**erythropoiesis**).

By approximately 6 weeks of gestation, the skeleton is rapidly developing and visually noticeable with imaging instrumentation. Bone continues to grow until early adulthood, complementing the growth of other body tissue. Up until this point bones grow in both length and diameter. However, around this time, the growth of longer bones, such as the femur, humerus, tibia, and fibula, ceases, and the adult height is realized. Some of the bones of the lower jaw and nose continue to grow throughout an individual's life, although the rate of growth slows dramatically.

The longest, heaviest, and strongest bone in the human body is the femur, which in an adult is about one-fourth of an individual's height. It is designed to handle

TABLE 1.7 Organ Systems

Organ System	Tissue or Organs Involved
Integumentary	Skin, hair, nails, sense receptors, oil glands
Skeletal	Bones and joints
Muscular	Muscles
Nervous	Brain, spinal cord, nerves
Circulatory	Heart, blood vessels
Lymphatic	Lymph nodes, lymph vessels, thymus, spleen, tonsils
Respiratory	Nose, pharynx, larynx, trachea, bronchi, lungs
Digestive	Mouth, teeth, salivary glands, tongue, pharynx, esophagus, stomach, small intestine, large intestine, rectum, anal canal, liver, gallbladder, pancreas
Urinary	Kidneys, ureters, urinary bladder, urethra
Reproductive (male)	Testes, ductus deferens, urethra, prostate, penis, scrotum
Reproductive (female)	Ovaries, uterus, uterine (fallopian) tubes, vagina, vulva, breasts

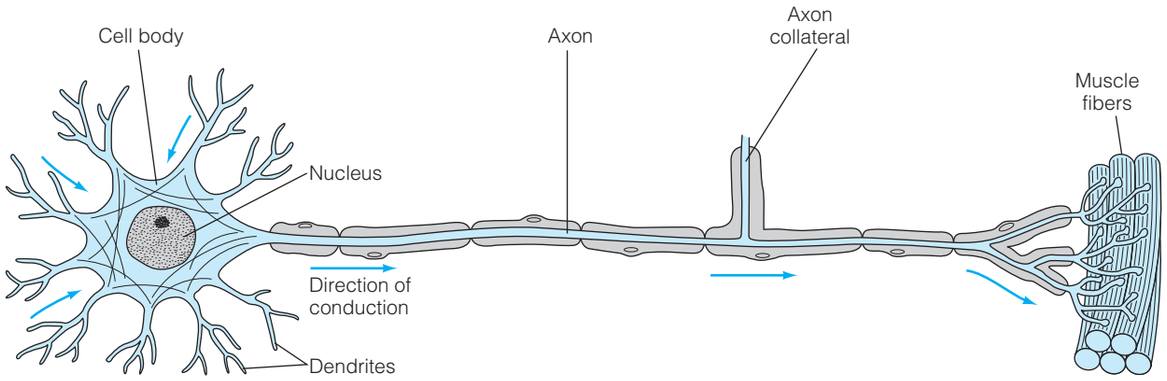


FIGURE 1.22 **General Neuron Structure**

physical stresses, such as vigorous jumping, greater than 280 kilograms per square centimeter (approximately 2 tons per square inch). Meanwhile, the three small bones in the inner ear are among the smallest bones. The pisiform bone of the wrist is very small as well, having a size approximate to that of a pea.

Bone contains several different types of cells, which are supported by a thick fluid called the **organic matrix**. The organic matrix is about 90% to 95% collagen protein, with the remainder being a homogeneous medium called ground substance. The collagen fibers are typically oriented along lines of tensile force, which provides bone with its tensile strength. The ground substance contains extracellular fluid with proteoglycans, especially chondroitin sulfate and hyaluronic acid. Also deposited within the organic matrix are mineral deposits called **hydroxyapatite**. Hydroxyapatite is composed of calcium and phosphate salt crystals: $Ca_{10}(PO_4)_6(OH)_2$. A typical crystal is about 400 angstroms long, 100 angstroms wide, and 10 to 30 angstroms thick. These crystals have the geometric shape of a long, thin plate. Magnesium, sodium, potassium, and carbonate ions are associated with hydroxyapatite crystals; however, they appear to be peripheral rather than an integral part of the structure. Small blood vessels also run throughout bone and deliver substances to and away from bone.

Bone is constantly experiencing **turnover**. That is, specific cells are constantly remodeling bone by absorbing and depositing bone components. **Osteoclasts**, which are large phagocytic cells, secrete proteolytic enzymes that digest proteins in the organic matrix, as well as acids (i.e., lactic and citric acids) that solubilize the minerals. In contrast, **osteoblasts**, found on the surface of bone, secrete bone components. Turnover allows bone to adapt or be remodeled according to the demands placed on it. For example, one of the benefits of weight training is an increased stress placed on bone, which then adapts by increasing its density. In contrast, prolonged exposure to zero gravity in space travel decreases the stress on bone and results in a loss of bone density.

Nervous Tissue

Nervous tissue is composed mostly of nerve cells (**neurons**), which serve as a very rapid communication system in the human body (**Figure 1.22**). The central nervous system includes the brain and spinal cord and represents the thinking and responsive portion of human nervous tissue. Links of neurons extend from the central nervous system to various organs and other tissue, thereby allowing for regulation of their function. Also, links of neurons extend to all skeletal muscle, allowing the central nervous system to initiate and control movement. Special neurons function as sensory receptors and are located in the skin and in sensory organs (e.g., tongue, nose, ears, eyes) and inside the body. These receptors send afferent impulses to the brain to provide information (e.g., pain, smell, taste, temperature) regarding the external and internal environment. Neurons are **excitable cells** that are able to respond to a stimulus by changing the electrical properties of their plasma membrane. Only muscle and nerve cells possess this ability and thus are deemed excitable.

Electrolytes are dissolved in extracellular and intracellular fluids. However, their concentrations are unequal across the plasma membrane (see Table 1.3). The concentrations of sodium (Na^+), chloride (Cl^-), and calcium (Ca^{2+}) are greater in the extracellular fluid, whereas the

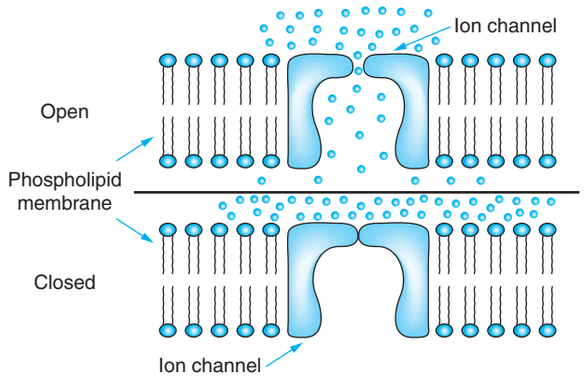


FIGURE 1.23 Ion Channel. The regulated opening of ion channels allows for rapid diffusion across the membrane.

concentration of potassium (K^+) is greater in the intracellular fluid. For instance, the concentration of sodium in the extracellular fluid is about 14 times greater than in intracellular fluid, whereas potassium is about 10 times more concentrated in the intracellular fluid relative to the extracellular fluid. The concentration differences provide the potential for electrolytes to diffuse across the plasma membrane through their respective ion channels when these are opened (**Figure 1.23**).

At rest, a leaking of potassium ions through channels allows for the development of a net negative charge in the intracellular fluid close to the plasma membrane and a positive charge in the extracellular fluid near the plasma membrane. This polarizes the membrane. The charge difference is referred to as the **resting potential**, which is –90 millivolts, as measured in the intracellular fluid. When neurons, as well as muscle (i.e., excitable cells), are stimulated, the resting membrane electrical potential is rapidly and transiently reversed and then returns to the resting state. This event, called an **action potential**, is propagated along the plasma membrane like a ripple on a pond.

Although some neurons are very long and may extend several meters or so, the trek of a neural impulse traveling either from a sensory neuron to the brain or from the brain to skeletal muscle or organs, or simply within the brain itself, requires the transmission of the impulse along several neurons linked together. An impulse reaching the end of one neuron is transferred to the next neuron by way of **neurotransmitters**. Numerous neurotransmitters are employed by nervous tissue, including serotonin, norepinephrine, dopamine, histamine, and acetylcholine. Terminal branches of neurons come in close contact with other neurons or tissue such as skeletal tissue or various

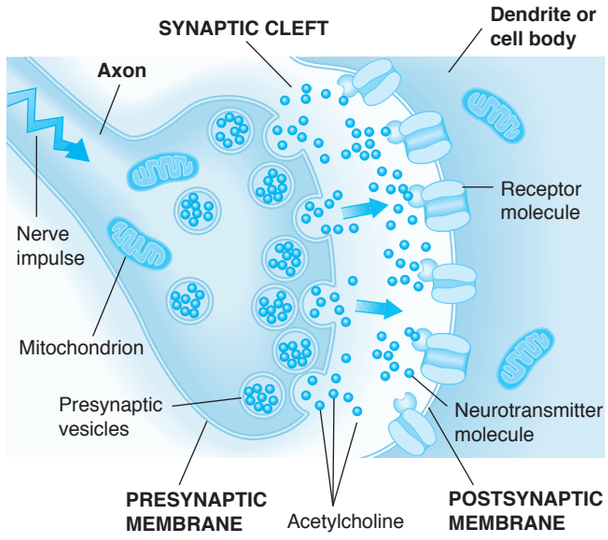


FIGURE 1.24 Axon Terminal Synapsing with Target Cell. The axon is shown. Neurotransmitter release and action on adjacent cells occur via receptor molecules on the postsynaptic membrane. Here the neurotransmitter is acetylcholine, which will react with a receptor molecule on skeletal muscle cells and elicit an action potential.

organs (**Figure 1.24**). This near connection is the **synapse**. Neurotransmitters are released from the signaling neuron and interact with receptors on the receiving cell, as depicted in Figure 1.24. This can initiate or inhibit the firing of an action potential on that cell.

The brain is an organ that is very densely packed with neurons. It weighs about 1,600 grams in an adult man and 1,450 grams in an adult woman and is protected by the skull. It is designed to interpret sensory input and decipher other incoming information, to develop both short- and long-term memory, to originate and coordinate most muscular movement, and to regulate the function of many organs. The brain can be subdivided into the cerebral hemispheres; the diencephalon (thalamus, hypothalamus, and epithalamus); the brain stem (midbrain, pons, and medulla); and the cerebellum. Although nutrition is directly involved in the proper development and function of all these regions, certain locations are especially important. For example, the hypothalamus is discussed to a greater extent than other regions with respect to its involvement in appetite regulation.

The spinal cord is about 42 centimeters (17 inches) long and extends from the foramen magnum of the skull, is continuous with the medulla of the brain stem, and reaches the level of the first lumbar vertebrae. The

spinal cord in essence is a two-way neural impulse conduction pathway to and from the brain. It is encased by protective vertebrae.

Skeletal Muscle

Skeletal muscle is composed mostly of very specialized cells that have the ability to shorten or contract upon command by the motor cortex of the brain. Because these cells are very long, they are often referred to as muscle fibers. Each muscle fiber is encased in a fine sheath of connective tissue called the endomysium. Several fibers that are bundled up in parallel and encased in a connective tissue sheathing are called fascicles. The several fascicles are themselves bundled within dense, coarse connective tissue called the epimysium. Skeletal muscle is so named because it is anchored at both ends to different bones of the skeleton. One anchoring site is called the origin, where the bone is generally immobile; the other attachment is called the insertion, in which the pulled bone is moved.

Like neurons, skeletal muscle fibers are excitable. In fact, the excitability of skeletal muscle fibers is very similar to that of neurons. However, the end result of excitability in a muscle fiber is the contraction or shortening of that cell. There are two principal types of muscle fibers: type I (slow-twitch) fibers and type II (fast-twitch) fibers.

Light and electron microscopy provide insight regarding the structural differences between muscle fibers and other cells. Each muscle fiber contains hundreds to thousands of small fiberlike units called **myofibrils**. Myofibrils can account for as much as 80% of a muscle cell's volume. Each myofibril is a stalklike collection of protein (**Figure 1.25**). The predominant proteins are **actin** and **myosin**, which are referred to as thin and

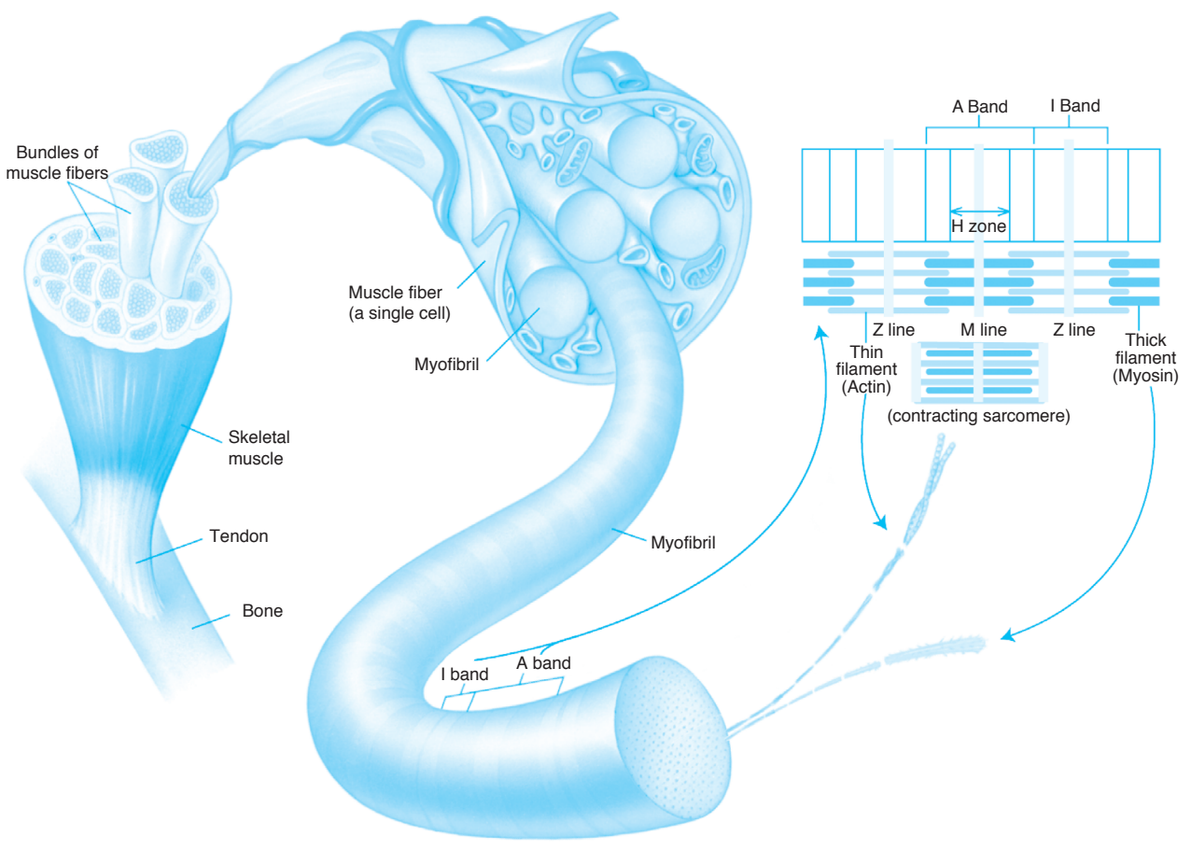
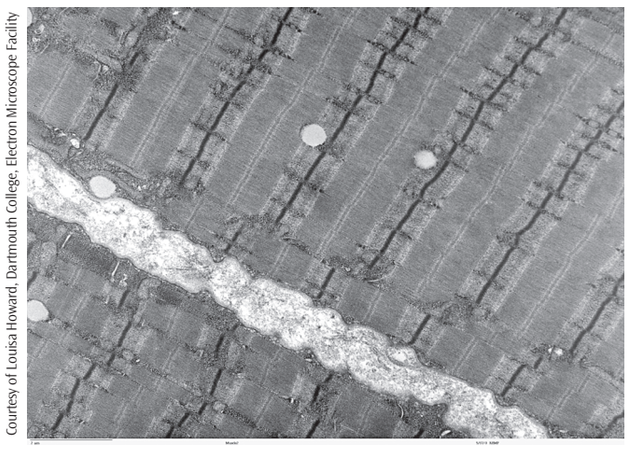


FIGURE 1.25 **Gross to Fine Organization of Skeletal Muscle Components**



Courtesy of Louisa Howard, Dartmouth College, Electron Microscope Facility

FIGURE 1.26 Electron Micrograph of Adjacent Sarcomeres (27,000×). Note the banding arrangement.

thick filaments, respectively. They are organized into a tiny contraction region called a **sarcomere** that sits next to adjacent and connected sarcomeres (**Figure 1.26**). Other proteins associated with the sarcomeres are **troponin** and **tropomyosin**. These proteins are involved in regulating the contraction of sarcomeres.

When skeletal muscle cells are stimulated, calcium (Ca^{2+}) ion channels open and calcium floods into the region of myofibrils and bathes the sarcomeres. Calcium enters the intracellular fluid from either the extracellular fluid or from storage within an organelle called the **sarcoplasmic reticulum**. Most of the calcium enters from the sarcoplasmic reticulum, which is a modified version of the smooth endoplasmic reticulum. Calcium then interacts with troponin proteins and initiates contraction by removing tropomyosin from the actin–myosin binding site (**Figure 1.27**). Myosin then slides actin fibers toward the center of the sarcomere, thereby shortening the sarcomere. The concomitant shortening of adjacent sarcomeres within a myofibril shortens the myofibril. Myofibrils in parallel shorten, thereby shortening a myofiber. The shortening of bundled myofibers allows for the shortening of a muscle as a whole.

For muscle fibers to contract, a lot of ATP must be used; some of the released energy is harnessed to power the contraction. ATP is also necessary for a contracted muscle cell to relax. When the stimulus is removed, ATP is needed to pump calcium out of the intracellular fluid of the muscle fiber into the sarcoplasmic reticulum or across the plasma membrane.

Heart, Blood, and Circulation

The adult heart is about the size of a fist and weighs about 250 to 350 grams. It serves to pump blood through miles and miles of blood vessels to all regions of the human body. Blood leaves the heart through the great arteries, namely, the aorta and pulmonary trunk, which feed into smaller arteries, which, in turn, feed into smaller arterioles and subsequently into tiny capillaries that thoroughly infiltrate tissue. Blood drains from capillaries into larger venules, which themselves drain into larger veins, which ultimately return blood to the heart. The blood is a delivery system. It delivers oxygen, nutrients, and other substances to cells throughout the human body. At the same time, blood serves to remove the waste products of cell metabolism (such as CO_2 and heat) from tissue. Capillaries are the actual site of the exchange of substances and heat between cells and the blood.

The heart consists of four chambers (two atria and two ventricles) and can be divided into a left and right half (**Figure 1.28**). The left half, consisting of the left atrium and ventricle, serves to receive oxygen-rich blood returning from the lungs and pump it to all tissue throughout the body. The right half of the heart, consisting of the right atrium and ventricle, serves to receive oxygen-poor blood returning from tissue throughout the body and pump it to the lungs. Therefore, the heart functions as a relay station for moving blood throughout the body in one large loop.

The heart is composed primarily of muscle cells that are mostly similar to skeletal muscle cells yet retain certain fundamental differences. Although most of the events involved in contraction of cardiac muscle are the same as skeletal muscle, the heart is not attached to bone. Furthermore, the heart does not require stimulus from the motor cortex to initiate contraction. The stimulus invoking excitability in the heart comes from a specialized pacemaker region called the atrioventricular (AV) node. The heart may beat in excess of two billion times throughout a human being's life.

The blood is composed of two main parts: solid cells and liquid plasma. **Erythrocytes** (red blood cells) function primarily as a shuttle transport for oxygen. **Hematocrit** is the percentage of the blood volume that is red blood cells. A typical adult hematocrit may be 40% to 45%. **Plasma** constitutes about 55% of the blood. About 92% of the plasma is water, while the remaining 8% includes over 100 different dissolved or suspended substances such as nutrients, gases, electrolytes, hormones, and proteins, such as albumin and clotting factors.

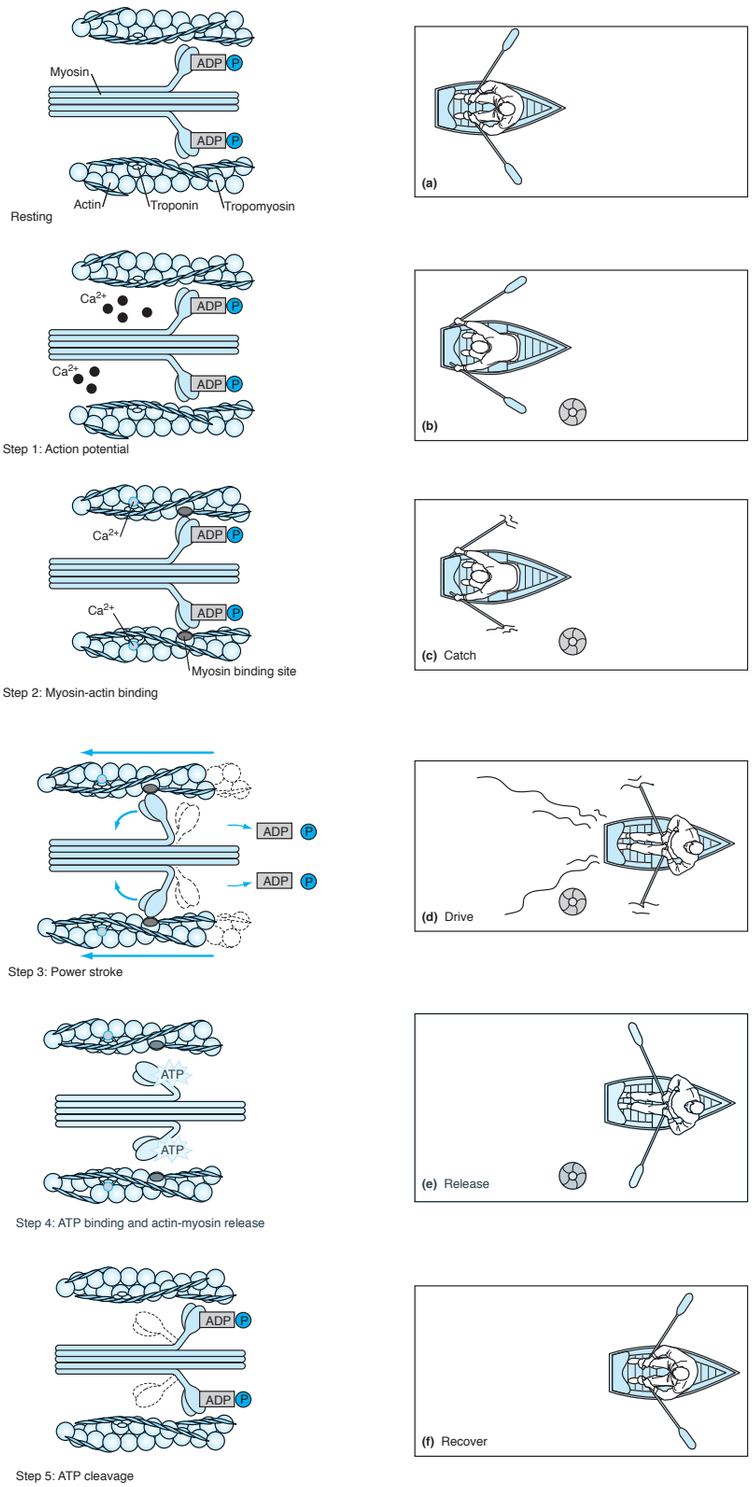


FIGURE 1.27 **Calcium Binding to Troponin.** Calcium binding to troponin results in the movement of tropomyosin and the revealing of myosin binding sites on actin. This allows myosin to bind and myofibrils to contract.

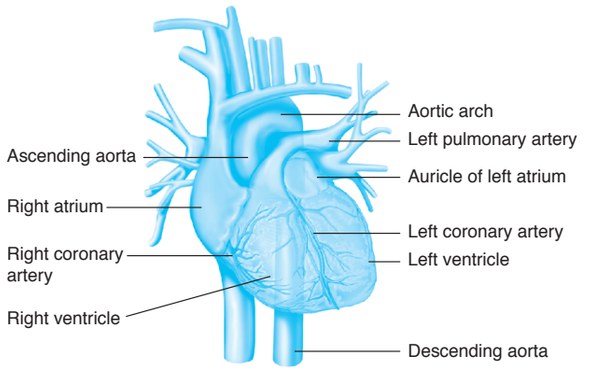


FIGURE 1.28 Human Heart. The major blood vessels are also shown.

The remaining components of blood are the **leukocytes** (white blood cells) and **platelets**, which collectively make up about 1% of blood. White blood cells are the principal component of the immune system and provide a line of defense against bacteria, viruses, and other intruders, whereas platelets participate in blood clotting.

Red blood cells transport oxygen throughout the human body. About 33% of the weight of a red blood cell is attributed to a specialized protein called **hemoglobin**. Hemoglobin is a large molecule that contains four atoms of iron. Hemoglobin's job is to bind to oxygen so that it can be transported in the blood. There are about 42 to 52 million red blood cells per cubic millimeter of blood, and each healthy cell contains about 250 million hemoglobin molecules. Because each hemoglobin molecule can carry four O_2 molecules, each red blood cell has the potential to transport one billion molecules of O_2.

When the heart pumps, blood is propelled from the right ventricle into the **pulmonary arteries** for transport to the lungs. Upon reaching the lungs and the pulmonary capillaries, CO_2 exits the blood and enters into the lungs. It is then removed during exhalation. At the same time, O_2 enters the blood from the lungs and binds with hemoglobin in red blood cells. The oxygen-containing blood leaves the lungs and travels back to the left side of the heart.

As the heart contracts, blood is pumped from the left ventricle into the **aorta**. Blood moves from the aorta into the arteries, then the arterioles, and finally into tiny capillaries in tissue. Blood that has perfused tissue is drained into small venules, which drain into larger veins and subsequently the vena cava. The blood leaving the heart is rich with oxygen, whereas the blood returning to the heart from tissue is relatively poor in oxygen. Carbon dioxide from tissue dissolves into the blood, with some being converted to carbonic acid via erythrocyte **carbonic anhydrase**. The venous blood is then pumped by the heart to the lungs to reload with O_2 and release CO_2. The measurement of the blood pumped out of the heart, directed toward either the lungs or body tissue, during one heart beat is the **stroke volume**. By multiplying stroke volume by heart rate, **cardiac output** can be determined.

Cardiac output	= Stroke volume	× Heart rate
(milliliters/minute)	(milliliters/beat)	(beats/minute)

Cardiac output is the volume of blood pumped out of the heart, either to the lungs or toward body tissue, in 1 minute. It should not matter which of the two destinations one considers because they occur simultaneously and will have a similar stoke volume of about 5 liters per minute. During exercise, both heart rate and stroke volume increase, which consequently increases cardiac output. In some people, cardiac output may increase as much as five to six times during heavy exercise. This allows for more oxygen-rich blood to be delivered to working skeletal muscle.

Under resting and comfortable environmental conditions, about 13% of the left ventricular cardiac output goes to the brain, 4% to the heart, 20% to 25% to the kidneys, 10% to the skin, and the rest to the remaining tissue in the body, such as the digestive tract, liver, and pancreas. During heavy exercise, a greater proportion of this cardiac output is routed to working skeletal muscle. This requires some redistribution of blood routed to other, less active, areas at that time, such as the digestive tract. In contrast, during a big meal and for a few hours afterward, a greater proportion of cardiac output is routed to the digestive tract, which steals a portion of the blood directed to areas having no immediate need, such as skeletal muscle.

Blood Pressure

Whether blood is in the heart or in blood vessels, it has a certain pressure associated with it. In fact, blood moves through the circulation from an area of greater **blood pressure** to an area of lower blood pressure. When the heart contracts, the pressure of the blood in the heart increases enough to drive the movement of blood throughout the circulatory system. Pressure is the force exerted upon a surface and is measured in millimeters

of mercury (mm Hg). Blood pressure is typically measured in a large artery, such as the brachial artery in the arm, and is expressed as systolic pressure over diastolic pressure. For instance, when blood pressure is measured at 120/80 mm Hg ("120 over 80"), the pressure exerted by systemic arterial blood is 120 mm Hg during left ventricular contraction (systolic) and 80 mm Hg when the left ventricle is relaxing (diastolic) between beats.

Renal System

Typically understated in function, the kidneys regulate the composition and volume of the extracellular fluid, which includes the blood. The two kidneys, along with their corresponding ureters, the bladder, and urethra, make up the renal (or urinary) system (**Figure 1.29**). Although the kidneys make up less than 1% of total body weight, they receive about 20% to 25% of the left ventricular cardiac output. Together the kidneys filter and process approximately 180 liters of blood-derived fluid daily.

Each kidney contains about one million **nephrons**, which are the blood-processing sites (**Figure 1.30**). Each nephron engages in two basic operations: (1) it filters plasma into a series of tubes, and (2) it processes the filtered fluid, reabsorbing needed substances while excreting unwanted or extra substances as urine. A relatively high capillary pressure (60 mm Hg) in the glomerulus drives the formation of plasma-derived fluid (**ultrafiltrate**) into the first aspect of the nephron tubule system, the Bowman, or glomerular, capsule. Ultrafiltrate is a water-based solution containing electrolytes, sulfites, bicarbonate, phosphates, amino acids, glucose, urea, creatinine, and other substances. Blood cells and most plasma proteins are too large and are not filtered.

The components of the ultrafiltrate have two possible fates: they are either reabsorbed into the blood or become part of urine. Normally the reabsorption of substances such as glucose and amino acids is extremely efficient. In contrast, the reabsorption of water and electrolytes involves hormonal regulation (e.g., aldosterone and atrial natriuretic polypeptide). The active processes in the renal tubule system engaged in reabsorbing glucose, amino acids, and some electrolytes require a significant amount of energy.

Of the 180 liters of fluid filtered and processed by the nephrons daily, less than 1% actually becomes urine. Thus, the reabsorptive processes of the kidneys are extremely powerful. Beyond regulating the composition of the extracellular fluid, the kidneys engage in other homeostatic operations. The kidneys are very sensitive to hypoxia of low oxygen level and secrete the endocrine factor erythropoietin, which stimulates erythropoiesis in bone marrow. Furthermore, renal parenchyma contains a vitamin D–metabolizing enzyme that converts a less active form of vitamin D to its most active form.

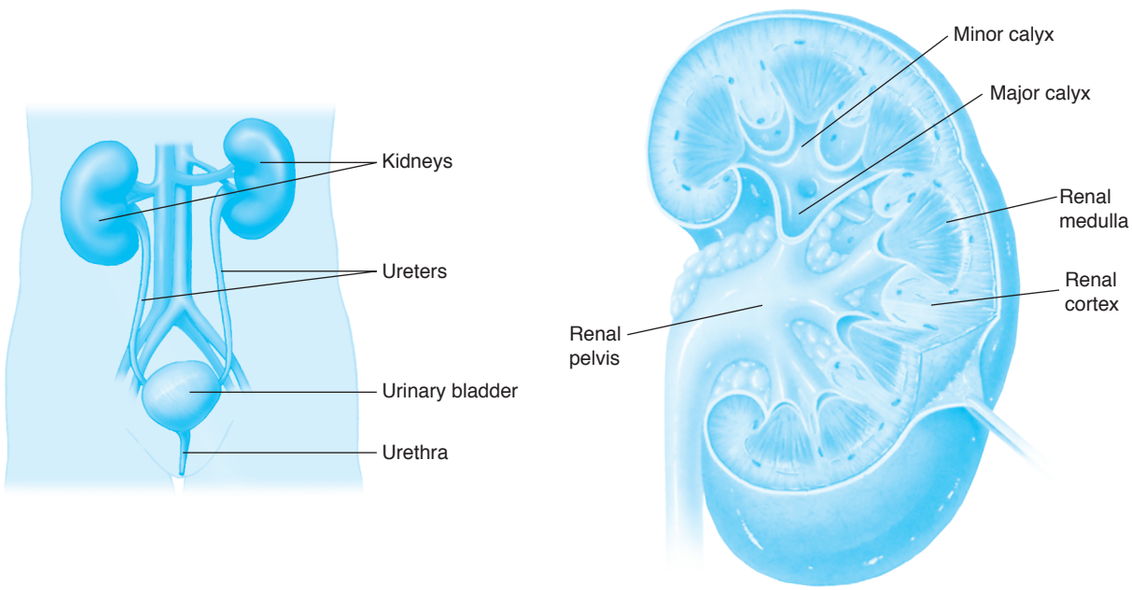


FIGURE 1.29 **The Urinary System**

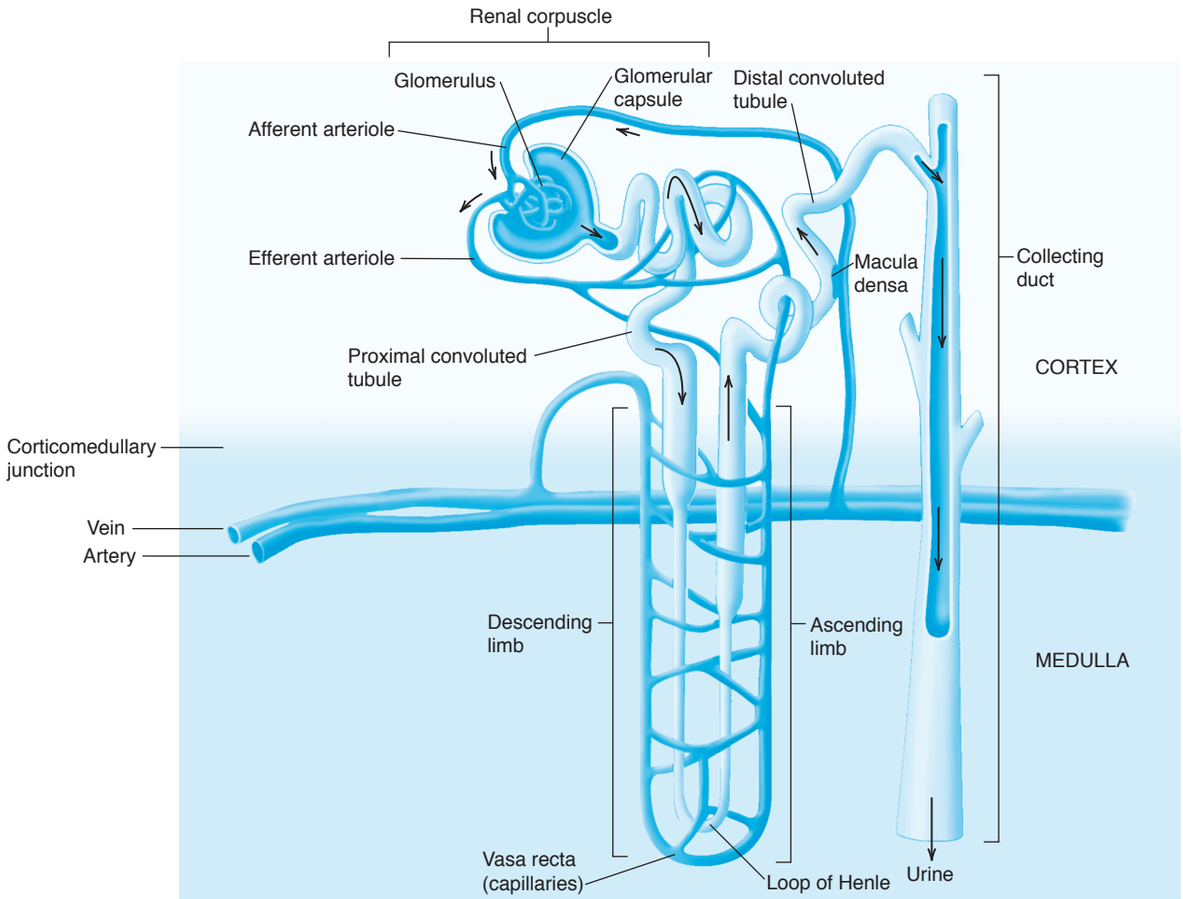


FIGURE 1.30 The Nephron. The basic structure of the nephron and its relation to the renal cortex and medulla, along with the blood supply, are shown. The Bowman (or glomerular) capsule, the proximal and distal tubules, the loop of Henle, and collecting ducts compose the nephron.

BEFORE YOU GO ON . . .

1. Within what tissue is red blood cell production most likely to occur?
2. What is cardiac output, and how is it calculated?
3. What is meant by the term *AV node*?
4. What mineral plays a key role when muscle is stimulated to contract?
5. List the proteins associated with the sarcomeres of muscle.

Summary

1. Fifty-five percent to 60% of the adult human body is composed of water; the remainder is protein and lipid.
2. The human body has more than 200 cell types, each of which has specialized functions but identical DNA.
3. Cell membrane and organelle membranes are composed of a bilipid layer. Cell membranes are 50% protein.
4. Carbohydrates may be part of a cell membrane linked to a protein to form a glycocalyx.
5. Ribosomes are the site of protein synthesis and are found in the endoplasmic reticulum.

6. Connective tissue, bone, cartilage, and tendons are composed of proteoglycan and chondroitin sulfate, which are synthesized in the Golgi apparatus of the cell.
7. Tissues with a high dependence on aerobic metabolism or fatty acid oxidation have more mitochondria.
8. Protein synthesis is dependent on DNA and RNA. Replication, transcription, translation, and post-translational modification are coordinated events within cells to produce unique proteins for each gene.
9. Mitochondrial DNA encodes for 13 of the 67 protein subunits that compose the electron transport chain for ATP production.
10. Production of protein is a very energy-expensive process. For example, 500 ATP molecules are needed to form 500 amino acid–tRNA associations.
11. Proteins are important in the structure of the cell, as cell receptors and hormones, in cell signaling, and in transport of nutrients across cell membranes.
12. Bone is mostly acellular; collagen is its major component.
13. Neurons are excitable tissue in which neurotransmitters such as serotonin, norepinephrine, dopamine, histamine, and acetylcholine are synthesized.
14. Skeletal muscle and cardiac muscle have specialized structures referred to as sarcomeres that possess a specialized protein involved with muscle contraction.
15. Oxygenation and disposal of waste from cells depends not only on cardiac function but also on an adequate cardiac output.

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