ADVANCED HUMAN NUTRITION

FOURTH EDITION

Denis M. Medeiros
Robert E. C. Wildman

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To my wife, Susan, for her patience and love; and my mother, Rita Wilkie, a proud member of "the greatest generation," for her belief in higher education. Also to my daughter, Kathryn, my stepfather, the late William P. Wilkie, and my father, the late Joseph Medeiros, for their support and love through the years.

–D.M.M.

To my children: Gage and Bryn for your love, patience, and support. Also, to my father, Dave, and nephew, Jack, as well as eternal inspiration from my brother, David, and my mother, Carol.

–R.W.

Brief Contents

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Preface

In the preface to the last two editions, we posed the question, "Why a book on advanced human nutrition?" We responded that there was, and continues to be, a limited number of intermediate and advanced textbooks that detail why nutrients are important from a biochemical, physiologic, and molecular perspective. Today, the same shortage exists with the exception of *Advanced Human Nutrition,* whose initial success and adoptions exceeded our expectations.

Nutrition is a relatively new science, having evolved from several other scientific disciplines in the 20th century, and it continues to evolve today. The expansion of nutritional knowledge has been astounding. At the beginning of the 20th century, work conducted on food and food components was carried out by only a handful of scientists. As the 20th century progressed into its first few decades, many of the now well-known vitamins were discovered, their structures defined, and synthesis techniques developed. The metabolic mechanisms of macronutrients, particularly carbohydrates, lipids, and proteins, as well as energy metabolism in general, became the subject of intense research. The scientists who carried out such research came from a wide variety of disciplines, including organic and inorganic chemistry, agricultural chemistry, physiological chemistry, medicine, and animal sciences.

Originally, nutritional research was conducted by men and women simply for the love of science. Later, during the 1940s, the federal government took a more active role in scientific research, including nutrition. A high rate of rejection of military conscripts due to nutrition-related conditions prompted the establishment of the first U.S. Recommended Dietary Allowances (RDAs) in 1941. The RDAs have continued to be modified ever since; the Dietary Reference Intakes (DRIs) are the most recent version.

Research had been carried out with the indirect support of the federal government before the establishment of the RDAs. Nutrition research occurred at the land-grant institutions created by Abraham Lincoln in the 1860s through the Morrill Act. Modern nutrition evolved from agricultural, medical, and basic sciences into a discipline of its own. One of the early fathers of nutrition was a Kansas native, E. V. McCollum, who introduced the laboratory rat as a useful model in scientific research when studying vitamin A. Similarly, poultry scientists used chicks as a research model and made contributions to medical sciences. Much of the research on fiber began with animal scientists studying forages and feeds of livestock.

Research pertaining to minerals, their composition in the human diet, and their physiologic roles took form in the 20th century. Most of the earlier mineral research efforts focused on the major minerals, such as calcium, phosphorus, sodium, potassium, chloride, and magnesium. However, some work relating to the role of iron and the development of iron deficiency appeared in the earlier decades of the 20th century.

In the 1960s and 1970s, rapid advances in technology allowed for the ability to detect small quantities of trace minerals, such as selenium, zinc, copper, iron, fluoride, chromium, manganese, and iodine. Although the role of iodine in preventing goiters was already known, as was the potential for deleterious health effects from selenium toxicity, there was limited information on the role of many trace elements in optimizing human health. New technologies, such as neutron activation and atomic absorption spectrophotometry, allowed for detection of trace minerals in the part-per-billion or microgram-per-liter range. An explosion of knowledge regarding trace minerals occurred in the latter part of the 20th century.

As the 20th century came to a close, it was known that many nutrients functioned at the gene level, an idea that was unheard of at the beginning of the 20th century. Today, in the 21st century, new research was and is currently being carried out on the identification of new compounds in the diet, such as plant chemicals (phytochemicals). This area has led to the identification of compounds that promote health and prevent disease.

Approach of this Text

In all of our previous editions, we sought to use a conversational approach in our writing to allow the reader to better grasp nutritional concepts, as opposed

to the more encyclopedic writing style common among advanced texts in science disciplines. We have been mindful of pedagogical tools that facilitate student learning. Many students have not mastered the optimal manner in which to read a textbook compared with literary works. A student needs to comprehend what he or she reads. Each chapter contains a series of "Before You Go On…" features in which the reader is asked a series of questions that can be answered from the material covered in the previous section. This tool can be used to help the student comprehend and focus on what is important in the text and to develop better study skills. The student is urged to answer each of the questions before proceeding with the next section of the chapter.

In the third edition of the text, two additional chapters were developed: one on fiber, which was previously part of the carbohydrates chapter; and a second on nutraceuticals and functional foods. Nutraceuticals—nutrients in foods that provide physiologic benefit beyond basic daily needs and/or support disease prevention or treatment—have been studied extensively in the last 15 years, and much has been discovered about their health benefits and mechanism of action. Fiber is one group of phytochemicals (plant-based nutraceuticals) where this information has expanded. Phytochemicals have been used to develop and produce functional foods either as supplements or as food. Thus, separate, in-depth attention to each of these still-evolving topics is needed for the student of nutrition to stay current. We include updated material to these two chapters.

As we did in previous editions, chapters are developed further by combining the scientific basis of why the basic nutrients are required with some applied concepts throughout. We accomplished this by integrating "Special Features" on focused topics to add depth to the chapters and to allow the student to view applications of the basic science. New special features have been added to this edition and existing ones have been updated based on new information in the scientific literature. The first edition was designed both as a textbook and a reference book, but the second, third, and now fourth editions are clearly designed as textbooks for college-level courses in human nutrition. The book assumes that students have completed courses in introductory nutrition, biochemistry, and some anatomy and physiology. Many students who are dietetics and nutrition majors, or who are beginning Master of Science degrees, will find this book appropriate for their level.

We have updated the figures and redesigned the text with the student in mind so that visual and textual, comprehension and study tools are available to reinforce concepts. This new edition has even more figures than the *Third Edition*; these were added after consultation with professors throughout the United States who are actively teaching advanced human nutrition courses, some of whom had been using the previous editions and some of whom had not. The goal here was to broaden the scope of concepts deemed significant for the student to comprehend. However, we took extra care to design the figures to balance simplicity with sufficient detail needed for an advanced treatment of the content.

Organization of this Text

Chapter 1 starts with an overview of the cell and examples of how nutrition can play a role in human health. **Chapter 2** is aimed at a rigorous review of the anatomy and physiology of digestion. Both of these chapters are the foundation on which the rest of the book is built. **Chapter 3** focuses on carbohydrates. However, as in the previous edition, fiber is discussed separately in **Chapter 4**. **Chapters 5 and 6** focus on lipids and proteins, respectively, with the latter becoming one of the highest profile nutrient areas at this time. **Chapter 7** focuses on water as a separate nutrient because it is present in our bodies in the largest quantity of all nutrients. **Chapters 8 and 9** focus on energy, weight control, and exercise. **Chapters 10 and 11** are detailed discussions of the fat-soluble and water-soluble vitamins, respectively. The text proceeds with two chapters on minerals: **Chapter 12** on major minerals and **Chapter 13** on minor minerals. We have added quite a bit of updated information to **Chapters 10 through 13** in response to our peer reviewers. **Chapter 14**, titled, "Nutraceuticals and Functional Foods," proved to be popular by adopters in the *Third Edition*. There have been scores of textbooks written on this topic. For this text, the focus was on understanding what constitutes nutraceuticals and functional foods, how they can be classified, and the nutrient categories of various types.

New to the *Fourth Edition*

Some of the most significant updates to the *Fourth Edition* include the following:

- Each chapter concludes with a section titled, "Clinical Insights," in which a topic of clinical relevance is presented, linking the basic nutrition science covered in each chapter. Future clinicians

will find this useful in connecting the basic and applied elements of human nutrition and dietetics, better preparing each student for future courses in clinical nutrition.

- The use of gene editing (referred to as CRISPR) is discussed in Chapter 1, as this technology has the potential to correct genetic mutations that impact nutrition utilization and metabolism.
- Diseases of the gastrointestinal tract that have nutritional relevance in health and disease are now covered in Chapter 2.
- Bariatric surgery procedures used to treat obesity are discussed in Chapter 2, as their popularity has increased in tandem with some potential nutrition problems.
- The controversy of a possible contributing factor to the obesity epidemic due to increased linoleic acid intake is debated in one of the Special Features in Chapter 5.
- Alcohol, as related to disease, is covered in Chapter 5.
- The new American Heart Association and American College of Cardiology algorithms to determine the risk of a cardiac event are included in Chapter 5.
- Protein requirements have been challenged by some scientists as it relates to the RDA, and Chapter 6 incorporates coverage of this controversy. Newly available methods that determine nitrogen requirements compared with traditional nitrogen balance methods have led some to conclude that the RDA for protein should be increased significantly.
- Protein intake, physical activity, and sarcopenia are discussed in Chapter 6.
- Clinical signs and treatment of dehydration are covered in Chapter 7.
- Energy requirements, as estimated by several different algorithms used in clinical settings, are included in Chapter 8.
- Exercise recommendations for both endurance and weight-bearing exercises are featured in Chapter 9.
- The implications of β-carotene cleavage by different enzymes in the small intestine are covered in Chapter 10.
- Coverage of the role of fat-soluble vitamins, particularly vitamin E, in Alzheimer's disease is included in Chapter 10.
- Transport mechanisms for water-soluble vitamins are discussed in Chapter 11.
- Novel roles of phosphorus in nutrition are featured in Chapter 12.
- The health-promoting effects of a group of phytochemicals—stilbenes—are now discussed in Chapter 14.

Instructor Resources

Comprehensive online teaching resources are available to instructors adopting the *Fourth Edition*, including the following:

- LMS-ready Test Bank, featuring more than 550 questions. This represents an increase of more than 100 questions compared with the previous edition. The level of rigor for each question is now indicated.
- Instructor's Manual, including Learning Objectives, Key Terms, Chapter Outlines, Discussion Questions, Lecture Notes, and In-class Activities. These have been heavily revised from previous editions.
- Slides in PowerPoint format, containing more than 750 slides that can be adapted for in-class lectures. For each topic, sample lectures with PowerPoint slides are included to help save time for the instructor in preparation of class materials. These lectures can be modified easily for each instructor's unique needs.
- Image Bank in PowerPoint format, compiling the figures appearing in this text.

In Conclusion

The order and content of information presented in this book are typical of the curricula at most academic institutions where nutrition and dietetics are taught. Both authors have had experience teaching this information in advanced nutrition courses and the materials included come from years of experience. We expect this course to provide students with the necessary skills and background to pursue higher-level nutrition classes; it can also serve as a capstone class. As we stated in the prefaces of previous editions, we continue to believe that students who use this text will go on to research careers in nutrition, perhaps even making contributions to the field that we will then cover in future editions of this text. There are those who used the *First Edition* of this book and went on to have research careers in nutrition and dietetics, and their findings are reported in this edition. We certainly look forward to and encourage such important works from future students.

Denis M. Medeiros

Robert E. C. Wildman

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Denis M. Medeiros, PhD, RD, LD, received his PhD in nutrition from Clemson University in 1981, his MS in physiology from Illinois State University in 1976, and his BS degree from Central Connecticut State University in 1974. He has been on the faculties of Mississippi State University (1981–1984), the University of Wyoming (1984–1989), The Ohio State University (1989–2000), and Kansas State University (2000–2011). He is currently Dean Emeritus of the Graduate School and Professor Emeritus of Molecular Biology and Biochemistry at the University of Missouri at Kansas City. Formerly, Dr. Medeiros was full professor and head of the Department of Human Nutrition, as well as associate dean for scholarship and research, at Kansas State University. He holds the rank of Professor Emeritus of Food, Nutrition, Dietetics, and Health and Associate Dean Emeritus for Scholarship and Research at Kansas State University. He was a former associate dean for research and dean of the College of Human Ecology at The Ohio State University. He has also spent time as a visiting faculty member at the Medical University of South Carolina in Charleston, South Carolina, and at the Washington University School of Medicine in St. Louis, Missouri.

Dr. Medeiros's major research has focused on the role of trace minerals, particularly copper, on the integrity of the cardiovascular system, and on the role of iron in bone integrity. He has received more than $4 million in grants to support his research endeavors from such institutions as the National Institutes of Health, the U.S. Department of Agriculture, and the National Science Foundation. He has authored or coauthored more than 125 scientific peer-refereed articles. Additionally, he has served on numerous editorial boards of prominent journals and has held elective offices in scientific societies. He has taught classes, both at the introductory and advanced levels, for undergraduate students and has taught graduate-level courses throughout his career. In addition, Dr. Medeiros has received outstanding teaching awards for his efforts and is both a registered and licensed dietitian.

Robert E. C. Wildman, PhD, RD, LD, FISSN, received his PhD in human nutrition from The Ohio State University, his MS in foods and nutrition from The Florida State University, and his BS in dietetics and nutrition from the University of Pittsburgh. He is a fellow of the International Society of Sports Nutrition (ISSN) and is an adjunct faculty member in the Department of Food Science and Human Nutrition at Texas Woman's University in Denton, Texas. His major areas of research include nutrition application to metabolism, body composition, weight control and health, and athletic performance. He has authored or coauthored more than 30 papers and several nutrition books, including *The Nutritionist: Food, Nutrition, and Optimal Health* and *Sport and Fitness Nutrition*; he also edited the *Handbook of Nutraceuticals and Functional Foods*. Dr. Wildman is a registered and licensed dietitian with the Academy of Nutrition and Dietetics and is the creator of TheNutritionDr.com.

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 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. Those characteristics allow humans to move with agility 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 basic sense, humans are inhalation units, food processors, combustion units for energy molecules as well as storage facilities for excessive energy; and they possess waste removal and defensive systems, internal and external communication systems, locomotive capabilities, and have reproductive capabilities. All of those functions are founded on or influenced by nutritional intake.

Humans comprehend how to nourish the demands of the human body; at the very least, a basic understanding of just what it is that needs to be nourished. But where does one begin to understand this? 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 those 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 requires nourishment, while, at the same time, produces 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 uses approximately 27. Oxygen is the most abundant element in the human body, accounting for approximately 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

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
Phosphorous	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**

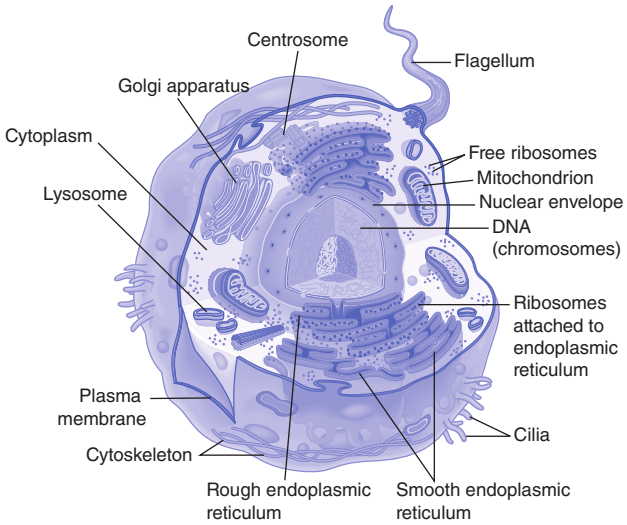

FIGURE 1.1 General Cell Structure. The figure shows the plasma membrane, cytoplasm, mitochondria, ribosomes, lysosomes, endoplasmic reticulum, Golgi apparatus, and the nuclear envelope.

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, approximately 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. **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 cellular structures and functions of both cell types are similar but with additional unique functions and roles (**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 1500 times. However, it was not until the advent of electron microscopy that the finer details of cells' **organelles** and ultrastructural aspects were scrutinized. Electron microscopy has the potential to expand imaging magnification up to 250,000 times.

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,

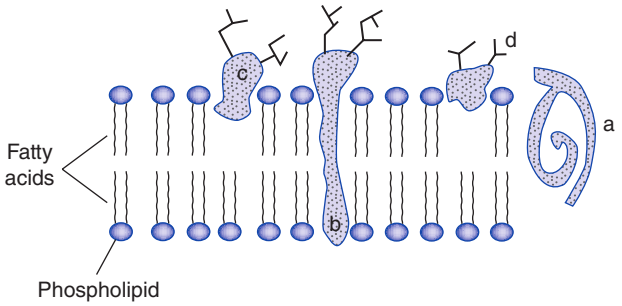

FIGURE 1.2 Membrane Structure: The Fluid Mosaic. A phospholipid bilayer (a) with associated proteins. Transmembrane proteins (b) can extend all the way through the membrane, such as the ion channel displayed. Peripheral proteins (c) are associated with only 1 side of the bilayer. Carbohydrate extensions (d) from membrane structures form the glycocalyx.

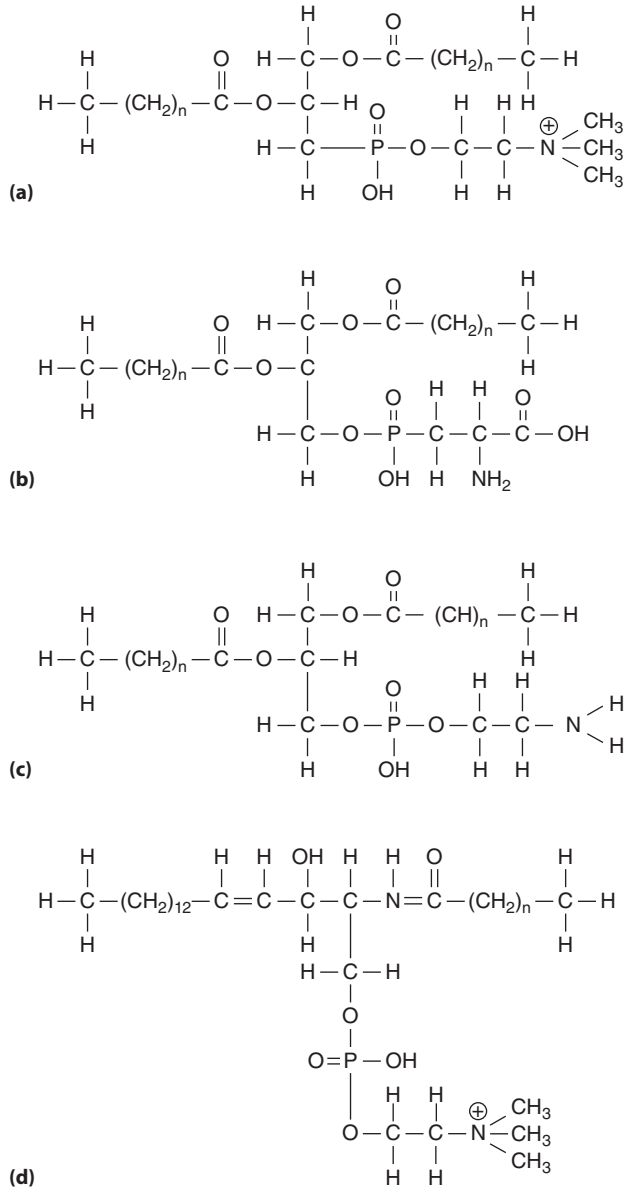

FIGURE 1.3 Phospholipid Molecular Structures. Phosphatidylcholine or lecithin (a), phosphatidylserine (b), phosphatidylethanolamine (c), and sphingomyelin (d).

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, approximately half of which are phospholipids. Cholesterol and glycolipids account for most of the remaining lipids. 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.

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 ion channels, carriers, active transporters, receptor bases, and enzymes. Typically, the portion of those 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.

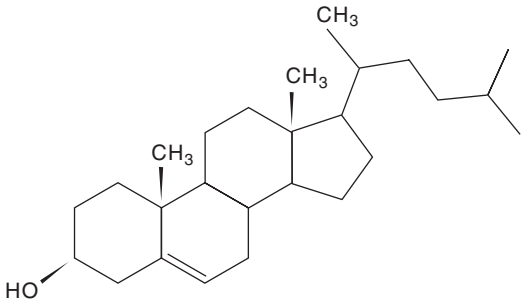

FIGURE 1.4 Cholesterol Molecule. Cholesterol is a planar molecule that enhances the stability of the plasma membrane. It is generally a hydrophobic molecule, with the exception of the hydroxyl group (OH).

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 that are either dissolved, suspended, or anchored within the watery medium. These substances include electrolytes, proteins, glucose and **glycogen**, amino acids, and lipids. The concentration of those 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 compared with the intracellular fluid. One function of integral membrane proteins is to pump certain substances against their concentration or diffusion gradients to maintain those 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 those 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
Biocarbonate (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 the 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, those 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.

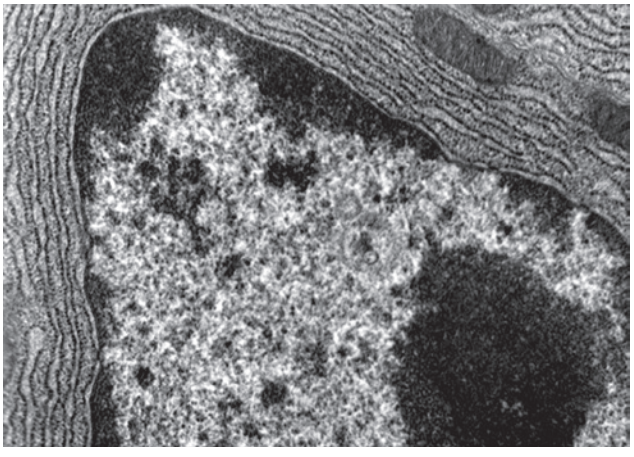

FIGURE 1.5 Rough Endoplasmic Reticulum. Electron micrograph of rough endoplasmic reticulum surrounding a nucleus (28,000×) showing the ribosomal studding.

Courtesy of Louisa Howard, Dartmouth College, Electron Microscope Facility.

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 the 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**. Those 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 a doubt its most famous attributes. As molecules, especially proteins, are manufactured in the endoplasmic reticulum, they are transported throughout the tubular system and destined to reach the agranular portion in closest proximity to the Golgi apparatus. At this location, small transport vesicles pinch off and transport those 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, those packets are

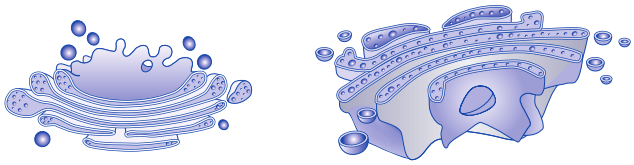

FIGURE 1.6 Golgi Apparatus. Budding of vesicles from the plasma membrane face of the Golgi apparatus. The vesicles generally contain substances that will be secreted from the cell.

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 those 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.

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. Those 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 typically between 250 and 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 approximately 800 mitochondria per cell. Likewise, the high ATP demands of muscle cells also require a rich complement of mitochondria. Mitochondria account for approximately 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 may 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 folded, which greatly expands its surface area. Along with the other phospholipids common to cellular membranes, diphosphatidylglycerol or cardiolipin is found in mitochondrial membranes,

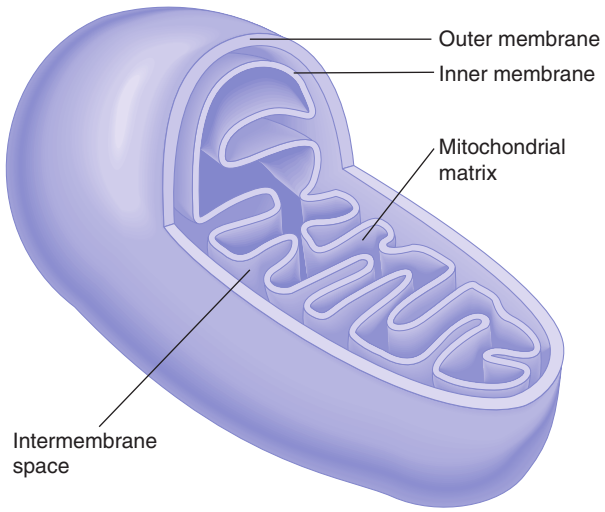

FIGURE 1.7 Mitochondrion. Note the inner and outer mitochondrial membranes.

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.

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 coactivator (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 coactivators. Both PGC-1α and PGC-1β 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 PGC-1α into C_2C_{12} cells (i.e., introduction of PGC-1α into cells) and into myocytes results in turning on mitochondrial biogenesis. PGC-1α may act as a coactivator of NRF-1, which then is thought to bind to the promoter of mtTFA to initiate the concomitant upregulation 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 those two transcription factors. It has also been reported that PGC-1α will up-regulate those two transcription factors. Upregulation of mtTFA augments mitochondrial biogenesis with those other transcription factors.

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.

BEFORE YOU GO ON . . .

1. Which cell compound is important for cell signaling?
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 which 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 continual with the matrix of the endoplasmic reticulum. Very large protein-associated pores penetrate the nuclear envelope, allowing molecules having a molecular weight of up to 44,000 daltons to move through the envelope with relative ease.

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 1 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). Those 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 1 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.

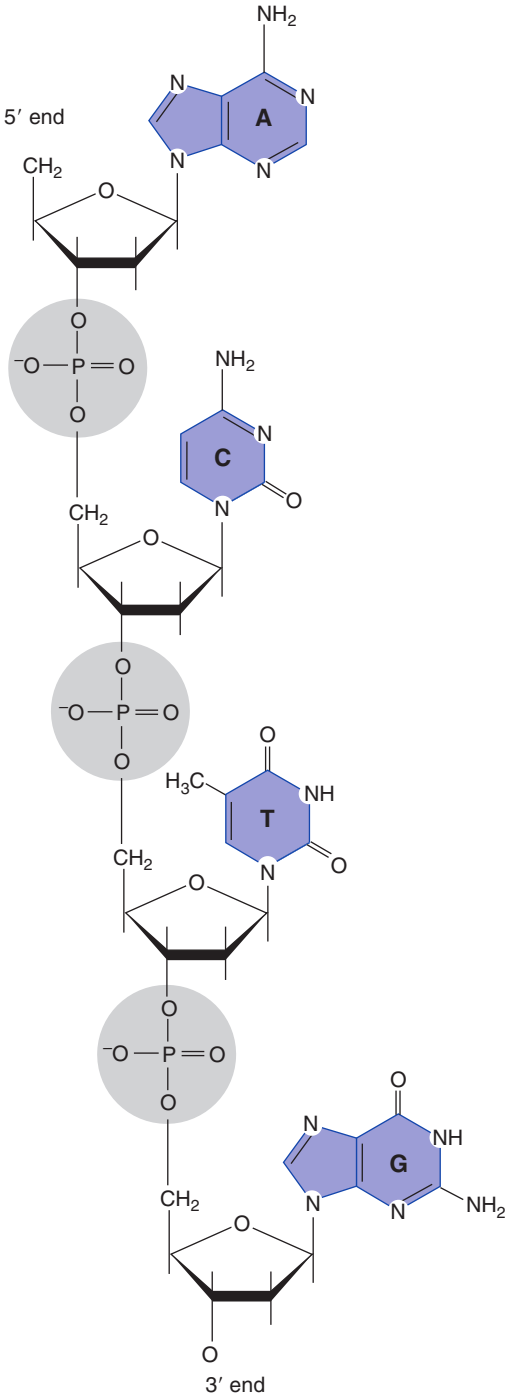

FIGURE 1.8 Single Strand of DNA. DNA bases linked by phosphodiester bonds, indicated by shaded areas.

Data from Doetsch, P. W. *Encyclopedia of Life Sciences*. John Wiley & Sons, Ltd., April 2001. [doi: 10.1038/npg.els.0000557].

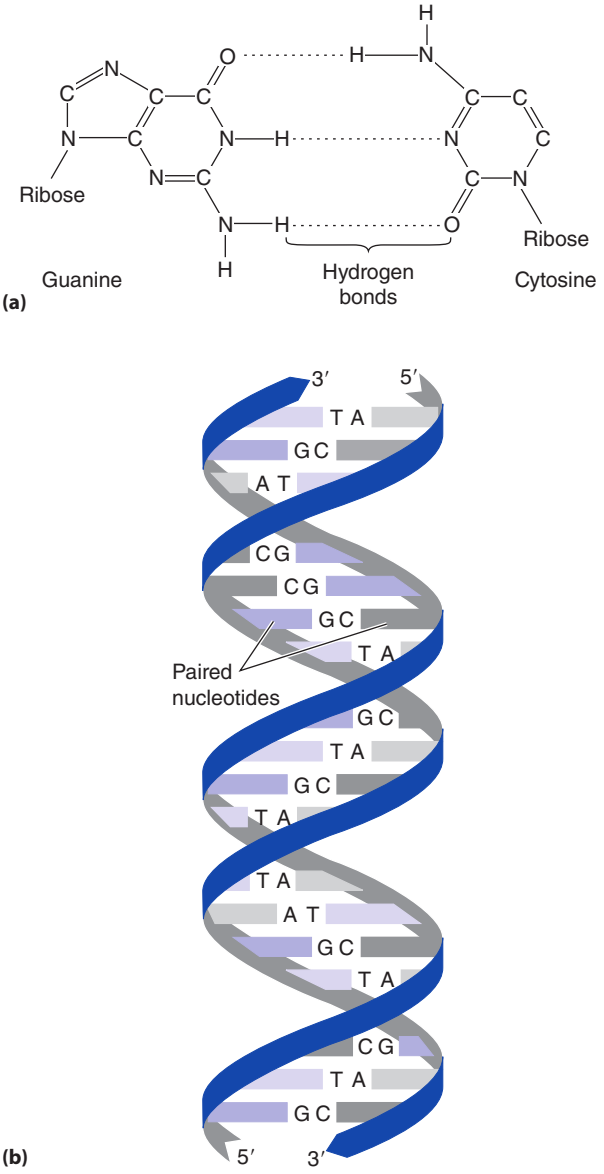

FIGURE 1.9 Hydrogen Bonding Between Complementary Nucleotide Bases. The hydrogen-bond link between adenine and thymine (a), and hydrogen bonding between the double helical DNA strands (b).

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

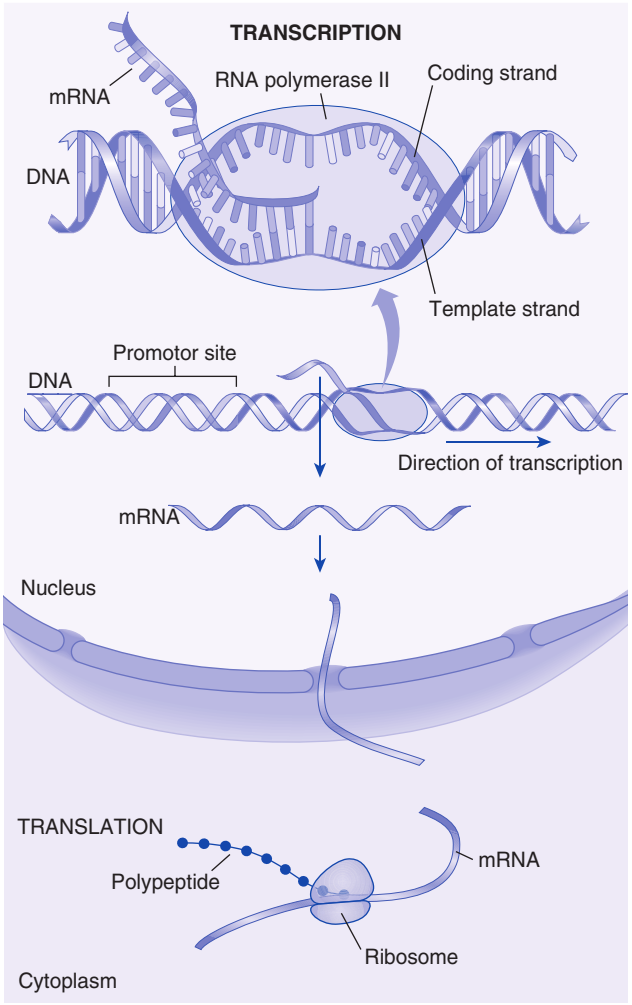

FIGURE 1.10 Protein Synthesis. Diagram of major steps in synthesis of protein as directed by DNA.

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 (**TABLE 1.5**).

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 **posttranscriptional 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

TABLE 1.5 Base-Pairing of Nucleic Acid Bases

DNA–DNA	DNA–RNA
A–T	A–U
C–G	C–G