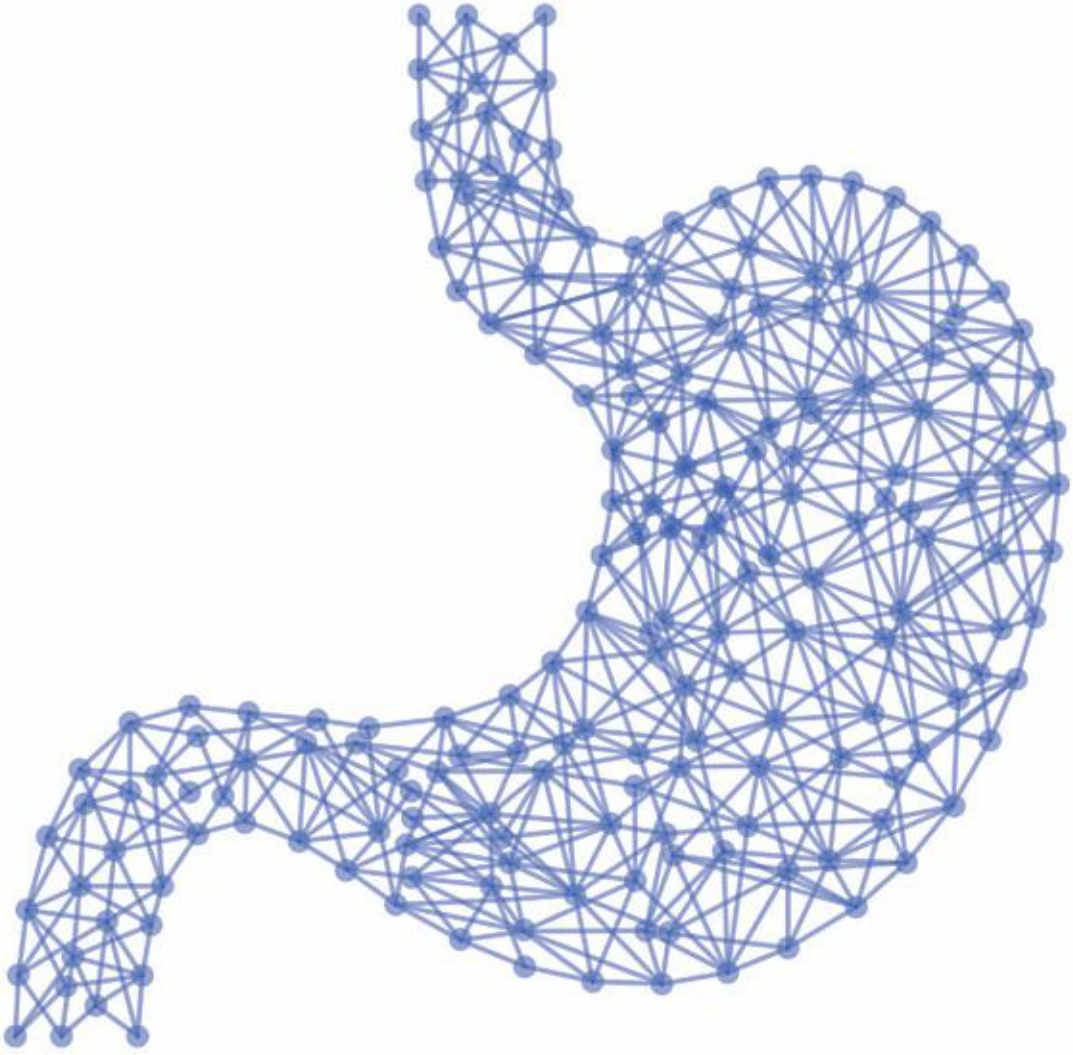
ADVANCED HUMAN NUTRITION

FIFTH EDITION

Denis M. Medeiros
Robert E. C. Wildman



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FIFTH EDITION

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To my wife, Susan, for her patience and love; and my mother, the late Rita Wilkie, my stepfather, the late William P. Wilkie, and my father, the late Joseph Medeiros, for their support and love through the years. All were proud members of "the greatest generation" and strongly believed in the value of higher education.

Also to my daughter, Kathryn, my three grandsons, sons (Abbas, Zain, and Essa), and my son-in-law, Hasan.

—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

Contents

Preface

In the preface to the last three 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 of previous editions 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, physiologic 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. The recommendations have changed for some nutrients over time as new research findings and discussions with scholars lead to a consensus of appropriate changes.

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. Eventually these scientists started to refer to themselves as a "nutritionist," "animal nutritionist," and "human nutritionist." A new profession evolved from the human nutritionists, as an area of applied human nutrition led to the field of dietetics. Dietitians became more involved with the link between food and nutrients with health and well-being, treatment of certain diseases, and development of diets for hospitalized patients.

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 (ppb) 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). Previously these nutrients had minimal attention and were treated as non-nutrients. Today, this attitude has changed. This area has led to the identification of compounds that promote health and prevent disease. This area is referred to as functional foods and nutraceuticals. Many of the food items identified or food items produced were once considered on the fringes of both science and nutrition. As you read this book, you will appreciate this area.

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. Additionally, it would be useful for students to work together and ask one another content questions to help develop full understanding. A new addition to this edition is the inclusion of 10 multiple choice questions following each 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, which previously was mentioned briefly. 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 mechanisms 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 have added 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. Another difference in this edition is that color has been added to the figures. This new edition has even more figures than the *Fourth 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. Some of the figures have been moved to different parts of each chapter to develop a better sequence to facilitate understanding.

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 "Food, Nutrients, Nutraceuticals, and Functional Foods," proved to be popular by adopters in the fourth edition. There have been scores of texts written on this topic. For this text, the focus is on understanding what constitutes nutraceuticals and functional foods, how they can be classified, the nutrient categories of various types, and government regulations.

New to the *Fifth Edition*

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

- As a fair number of students using this text are likely to be enrolled in a dietetics program, each chapter has a mini-case study where students are asked to suggest solutions to the nutrition problem presented. The instructor has a manual on suggestions and/or talking points to facilitate discussion of each case study.
- COVID-19 is a universal health problem where nutrition may have a role in protection. Chapters 1, 10, and 13 discuss the roles of vitamin D, zinc, and selenium in the in lowering the risk of mortality from infection.
- The microbiome of the large intestine is discussed in Chapter 2 as related to health. Research suggests that there are hundreds to thousands of different microbes that inhabit our large intestine.
- Diagrams of the liver, pancreas, and gallbladder are illustrated in Chapter 2 along with in-depth discussion of secretions of each as they impact digestion.
- Mediators of appetite in Chapter 2, such as α-melanocyte stimulating hormone and obestatin, are included.
- Dietary fiber in food products as defined by the CODEX Alimentarius Commission was established by the Food and Agriculture Organization of the World Health Organization (WHO), in part, to develop global food standards as detailed in Chapter 4.
- A discussion of lipoproteins in Chapter 5 is presented earlier in the chapter. This section has new figures developed to illustrate this complex area.
- 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 American Heart Association and American College of Cardiology have new algorithms to determine the risk of a cardiac event are included in Chapter 5.
- The impact of vitamin D upon the incidence of prostate cancer has been added to Chapter 10.
- Transport mechanisms for water-soluble vitamins are discussed in Chapter 11.
- A discussion of choline is presented in Chapter 11.
- A new diagram of the interactions of folic acid and vitamin B_{12} is in Chapter 11.
- Novel roles of phosphorus in nutrition are featured in Chapter 12.
- Micronutrient roles in modulating the severity of COVID-19 are explained in Chapter 13.
- The health-promoting effects of a group of phytochemicals—stilbenes—are now discussed in Chapter 14.
- Each chapter includes citations to supporting research studies and reviews that can be helpful to students wanting to investigate topics further.
- New four-color interior that serves to enhance the figures, provide visual and textual comprehension, and reinforces concepts.
- Additional online case studies based on real-world scenarios.
- New Appendix A: Dietary Reference Intakes.

Instructor Resources

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

- LMS-ready Test Bank, featuring more than 550 questions. The level of rigor for each question is 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

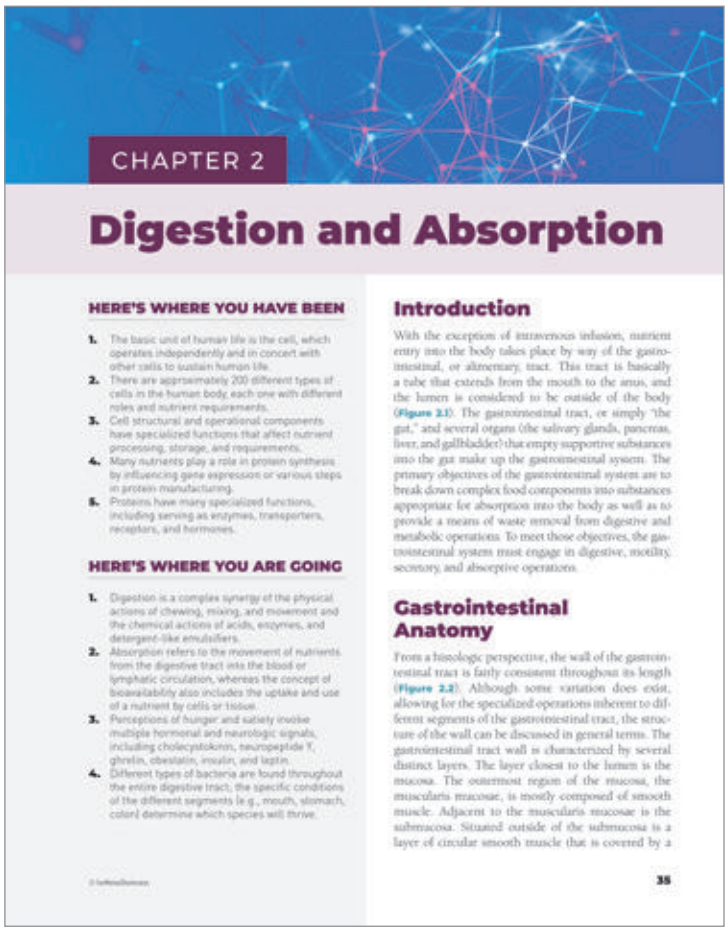
The order and content of information presented in this book are typical of the curricula at most academic institutions where nutrition and dietetics are taught. Both authors have had experience teaching this information in advanced nutrition courses and the materials included come from years of experience. 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

How to Use This Book

Chapter Features

- Each chapter opens with a **Here's Where You Have Been** box that lists key concepts that have already been addressed and a **Here's Where You Are Going** box that lists key concepts that will be discussed in the chapter.



CHAPTER 2

Digestion and Absorption

HERE'S WHERE YOU HAVE BEEN

1. The basic unit of human life is the cell, which operates independently and in concert with other cells to sustain human life.
2. There are approximately 200 different types of cells in the human body, each one with different roles and nutrient requirements.
3. Cell structural and operational components have specialized functions that affect nutrient processing, storage, and requirements.
4. Many nutrients play a role in protein synthesis by influencing gene expression or various steps in protein manufacturing.
5. Proteins have many specialized functions, including serving as enzymes, transporters, receptors, and hormones.

HERE'S WHERE YOU ARE GOING

1. Digestion is a complex synergy of the physical actions of chewing, mixing, and movement and the chemical actions of acids, enzymes, and detergent-like emulsifiers.
2. Absorption refers to the movement of nutrients from the digestive tract into the blood or lymphatic circulation, whereas the concept of bioavailability also includes the uptake and use of a nutrient by cells or tissue.
3. Perceptions of hunger and satiety involve multiple hormonal and neurologic signals, including cholecystokinin, neuropeptide Y, ghrelin, obestatin, insulin, and leptin.
4. Different types of bacteria are found throughout the entire digestive tract; the specific conditions of the different segments (e.g., mouth, stomach, colon) determine which species will thrive.

Introduction

With the exception of intravenous infusion, nutrient entry into the body takes place by way of the gastrointestinal, or alimentary, tract. This tract is basically a tube that extends from the mouth to the anus, and the lumen is considered to be outside of the body (Figure 2.1). The gastrointestinal tract, or simply "the gut," and several organs (the salivary glands, pancreas, liver, and gallbladder) that empty supportive substances into the gut make up the gastrointestinal system. The primary objectives of the gastrointestinal system are to break down complex food components into substances appropriate for absorption into the body as well as to provide a means of waste removal from digestive and metabolic operations. To meet those objectives, the gastrointestinal system must engage in digestive, motility, secretory, and absorptive operations.

Gastrointestinal Anatomy

From a histologic perspective, the wall of the gastrointestinal tract is fairly consistent throughout its length (Figure 2.2). Although some variation does exist, allowing for the specialized operations inherent to different segments of the gastrointestinal tract, the structure of the wall can be discussed in general terms. The gastrointestinal tract wall is characterized by several distinct layers. The layer closest to the lumen is the mucosa. The outermost region of the mucosa, the muscularis mucosae, is mostly composed of smooth muscle. Adjacent to the muscularis mucosae is the submucosa. Situated outside of the submucosa is a layer of circular smooth muscle that is covered by a

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Table 4.2 Fiber Types and Characteristics, Food Sources, and Bacterial Fermentability in the Gut

Fiber Type	Characteristics	Food Sources	Fermentability*
Soluble			
Pectins	Plant cell walls and middle lamella between cells; major fiber consumed	Fruits, especially citrus fruits, apples, bananas, and cherries; cabbage, potatoes, beans	High
Gums	Plant exudates, bacterial fermentation product	Dried beans, oats, fruits, bran, vegetables, seaweed, bacterial fermentation	High
Mucilages	Synthesized by plant cells	Typically a food additive	High
Fructans (inulin, oligofructose, and fructo-oligosaccharides)	Oligosaccharide	Chicory root, bananas, onions, agave, garlic, asparagus, jicama, and leeks; food additives	High
Insoluble			
Cellulose	Structural framework of green plants and algae	Lettuce, green leaves, stems, seaweeds, most plant sources	Low
Hemicellulose	Structural component of cell walls and binds to cellulose and pectin	Most plant sources, whole grains, bran	Low
Lignin	Mature cell walls	Vegetables, wheat, and other cereal grains	Low

*High and Low denote the relative degree of bacterial fermentation

- Each chapter includes **tables** and **figures** that highlight important information and demonstrate a variety of concepts.

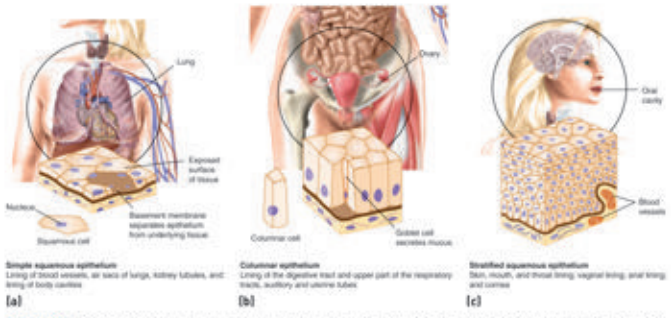


Figure 1.20 Epithelia. Different types of epithelia include simple squamous **(a)**, columnar **(b)**, and stratified squamous **(c)**. Cuboidal cells not shown.

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.

- **Before You Go On. . .** boxes act as knowledge check questions to test students on the concepts learned in each section of the text.

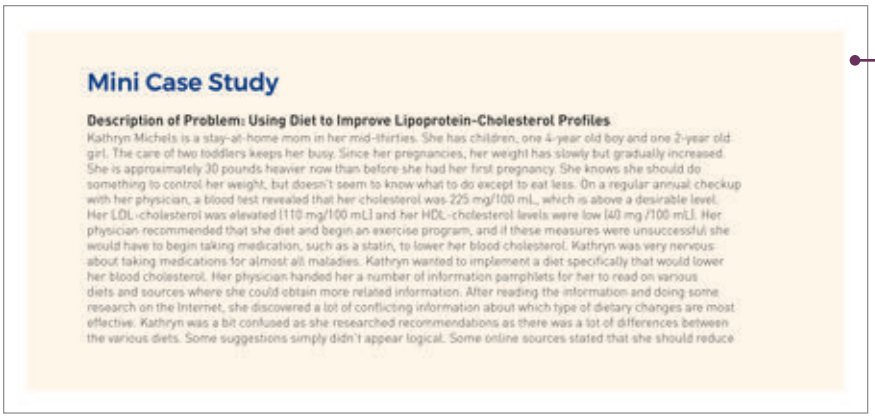
SPECIAL FEATURE 1.1 Mitochondrial Diseases

Genetic, metabolic, and dietary events can result in mitochondrial diseases. Many mitochondrial diseases are due to inborn errors of metabolism that result in dysfunction of the electron transport system.[4] 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.[4] 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.[4,5] The DNA responsible for encoding cytochrome c oxidase subunit IV is present, but not the DNA of mitochondria-encoded cytochrome c oxidase subunit II.[3] Another disorder, myoclonus epilepsy with ragged red fibers, 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 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. A copper chaperone protein, called SCO2, was found to be mutated in several forms of fatal infantile cardiomyopathy leading to cytochrome c oxidase deficiency.[4] 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,[5] a patient with SCO2 mutations had severe hypertrophic cardiomyopathy that was reversed with copper-histidine supplementation.

- **Special Feature** boxes can be found in every chapter and focus on topics that add depth and allow the student to view applications of the basic science learned.



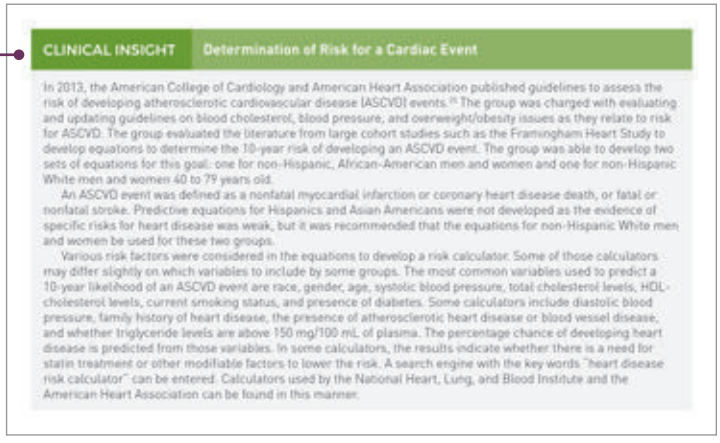
Mini Case Study

Description of Problem: Using Diet to Improve Lipoprotein-Cholesterol Profiles

Kathryn Michels is a stay-at-home mom in her mid-thirties. She has children, one 4-year old boy and one 2-year old girl. The care of two toddlers keeps her busy. Since her pregnancies, her weight has slowly but gradually increased. She is approximately 30 pounds heavier now than before she had her first pregnancy. She knows she should do something to control her weight, but doesn't seem to know what to do except to eat less. On a regular annual checkup with her physician, a blood test revealed that her cholesterol was 225 mg/100 mL, which is above a desirable level. Her LDL-cholesterol was elevated (110 mg/100 mL) and her HDL-cholesterol levels were low (40 mg /100 mL). Her physician recommended that she diet and begin an exercise program, and if these measures were unsuccessful she would have to begin taking medication, such as a statin, to lower her blood cholesterol. Kathryn was very nervous about taking medications for almost all maladies. Kathryn wanted to implement a diet specifically that would lower her blood cholesterol. Her physician handed her a number of information pamphlets for her to read on various diets and sources where she could obtain more related information. After reading the information and doing some research on the Internet, she discovered a lot of conflicting information about which type of dietary changes are most effective. Kathryn was a bit confused as she researched recommendations as there was a lot of differences between the various diets. Some suggestions simply didn't appear logical. Some online sources stated that she should reduce

- Each chapter has a **mini-case study** where students are asked to suggest solutions to the nutrition problem presented.

- Each chapter concludes with a **Clinical Insight** in which a topic of clinical relevance is presented, linking the basic nutrition science covered in each chapter.



CLINICAL INSIGHT Determination of Risk for a Cardiac Event

In 2013, the American College of Cardiology and American Heart Association published guidelines to assess the risk of developing atherosclerotic cardiovascular disease (ASCVD) events.[5] The group was charged with evaluating and updating guidelines on blood cholesterol, blood pressure, and overweight/obesity issues as they relate to risk for ASCVD. The group evaluated the literature from large cohort studies such as the Framingham Heart Study to develop equations to determine the 10-year risk of developing an ASCVD event. The group was able to develop two sets of equations for this goal: one for non-Hispanic, African-American men and women and one for non-Hispanic White men and women 40 to 79 years old.

An ASCVD event was defined as a nonfatal myocardial infarction or coronary heart disease death, or fatal or nonfatal stroke. Predictive equations for Hispanics and Asian Americans were not developed as the evidence of specific risks for heart disease was weak, but it was recommended that the equations for non-Hispanic White men and women be used for these two groups.

Various risk factors were considered in the equations to develop a risk calculator. Some of those calculators may differ slightly on which variables to include by some groups. The most common variables used to predict a 10-year likelihood of an ASCVD event are race, gender, age, systolic blood pressure, total cholesterol levels, HDL-cholesterol levels, current smoking status, and presence of diabetes. Some calculators include diastolic blood pressure, family history of heart disease, the presence of atherosclerotic heart disease or blood vessel disease, and whether triglyceride levels are above 150 mg/100 mL of plasma. The percentage chance of developing heart disease is predicted from those variables. In some calculators, the results indicate whether there is a need for statin treatment or other modifiable factors to lower the risk. A search engine with the key words "heart disease risk calculator" can be entered. Calculators used by the National Heart, Lung, and Blood Institute and the American Heart Association can be found in this manner.

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Denis M. Medeiros, PhD, RD(Ret) 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), Kansas State University (2000–2011), and the University of Missouri-Kansas City (2011–2017). 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. Dr. Medeiros has received outstanding teaching awards for his efforts. In addition to research grants, he obtained NIH training grants aimed at facilitating transfer of under-represented students from Kansas community colleges to Kansas State University.

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 as well as the founder of the International Protein Board (iPB).

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, and storage facilities for excess energy; in addition, they possess waste removal and defensive systems, internal and external communication systems, locomotive capabilities, and reproductive capabilities. All of those functions are founded on or influenced by nutritional intake.

Compared to other life science fields, nutrition is a relatively new science that is composed of many disciplines: biology and physiology, cell biology, chemistry and biochemistry, and agriculture sciences to name a few. These foundation disciplines gave rise to more applied sciences such as human and animal nutrition, dietetics, and food science. Humans comprehend how to nourish the demands of the human

body as a whole—or, 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. Cells compose our organs, and organs the various systems that compose us. 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. At the same time, each cell 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. Within each cell there are organelles and genetic materials that may be influenced by nutrients.

An understanding of cells, organs and the systems they compose, and biochemical and molecular events that are required for animal life is essential if we are to understand nutrition. This text integrates biology with nutrients that are required for life and promote health. This chapter reviews biologic processes needed to understand why and how nutrients promote life, and their roles in disease and health. At one time it was believed that nutrients functioned more as coenzymes in biochemical reactions. While this is true, we have a greater understanding of the role nutrients have at the molecular and gene levels. The student is encouraged to become familiar with the concepts presented in this chapter to be better prepared to learn the role of nutrients presented in subsequent chapters.

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 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

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**

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.[1] 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 1,500 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.

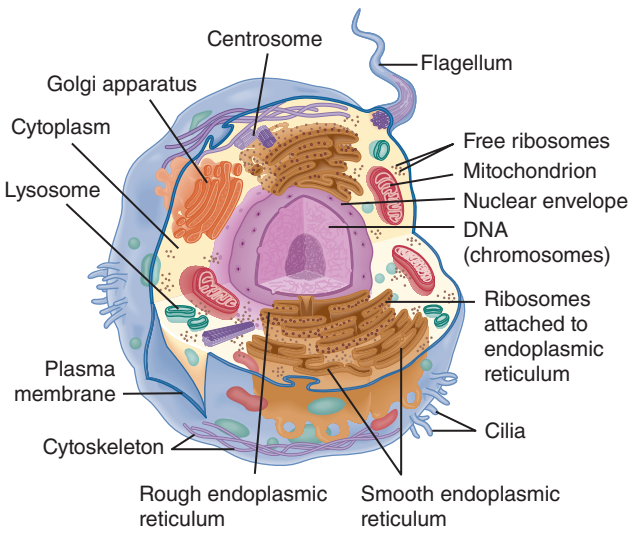


Figure 1.1 General Cell Structure. The figure shows the plasma membrane, cytoplasm, mitochondria, ribosomes, lysosomes, endoplasmic reticulum, Golgi apparatus, and nuclear envelope.

Plasma Membrane

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.

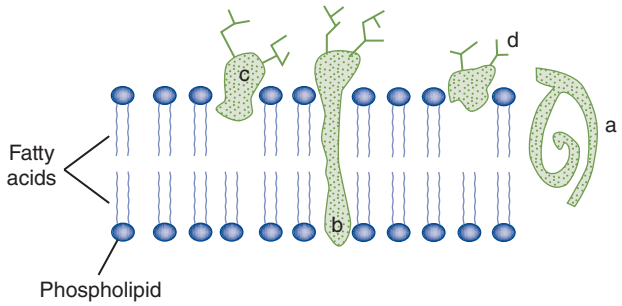


Figure 1.2 Membrane Structure: The Fluid Mosaic. A phospholipid bilayer **(a)** with associated proteins. Transmembrane proteins **(b)** can extend all the way through the membrane, such as the ion channel displayed. Peripheral proteins **(c)** are associated with only one side of the bilayer. Carbohydrate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

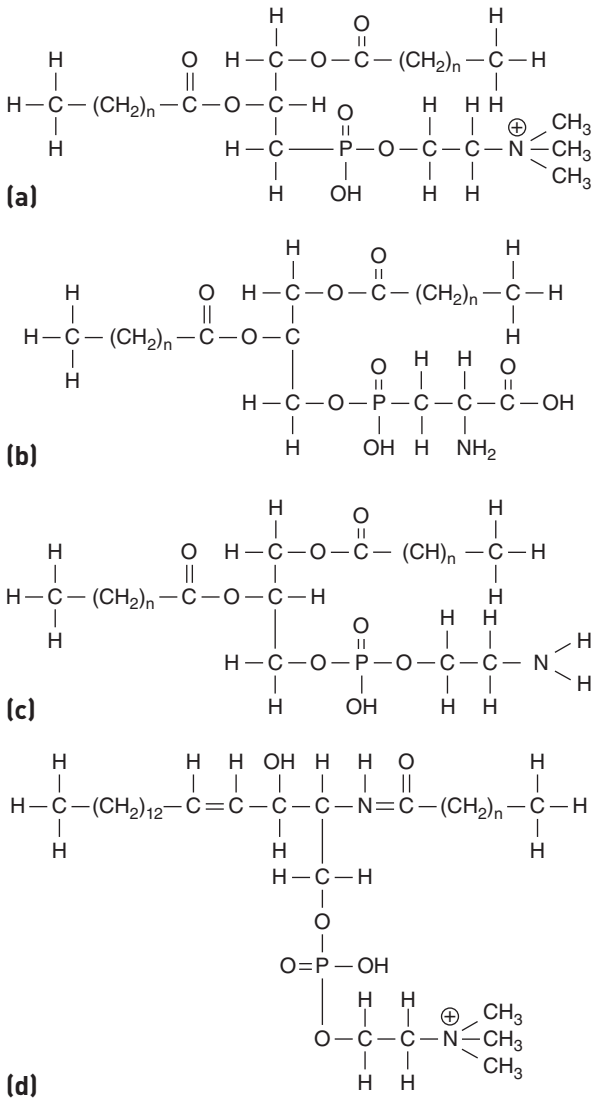


Figure 1.3 Phospholipid Molecular Structures. Phosphatidylcholine or lecithin **(a)**, phosphatidylserine **(b)**, phosphatidylethanolamine **(c)**, and sphingomyelin **(d)**.

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 its 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,

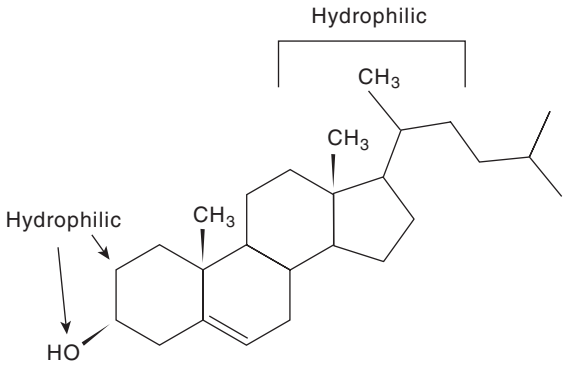


Figure 1.4 Cholesterol Molecule. Cholesterol is a planar molecule that enhances the stability of the plasma membrane. It is generally a hydrophobic molecule, with the exception of the hydroxyl group (OH).

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.

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

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.

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 highly specialized versions, 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.

Endoplasmic Reticulum

The **endoplasmic reticulum** is a tubular network that is situated adjacent to the nucleus. 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

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

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

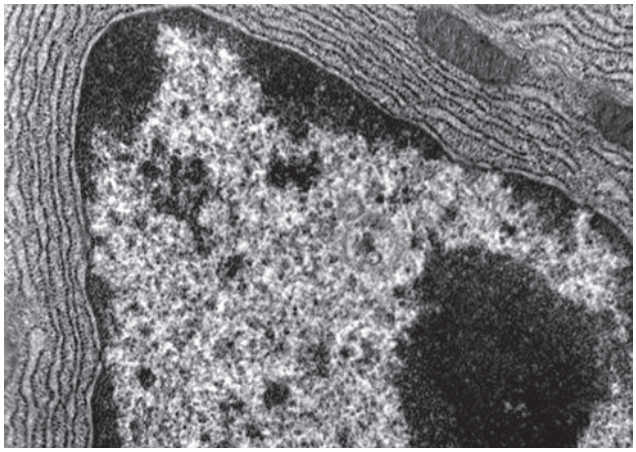


Figure 1.5 Rough Endoplasmic Reticulum. Electron micrograph of rough endoplasmic reticulum surrounding a nucleus (28,000×) showing the ribosomal studding.

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

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.

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.[2] 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 mucus 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

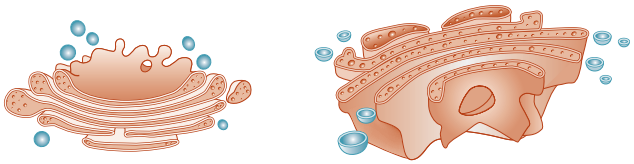


Figure 1.6 Golgi Apparatus. Budding of vesicles from the plasma membrane face of the Golgi apparatus. The vesicles generally contain substances that will be secreted from the cell.

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 next) and release their contents into the extracellular space in an exocytotic process. Because of this activity, those 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 those packets may be **hormones**, neurotransmitters, eicosanoids, or ductal secretions. Some of the concentrated packets are not destined for exocytosis; 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. 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; ribosomes, where protein synthesis occurs; or contractile myofibrils 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, 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.

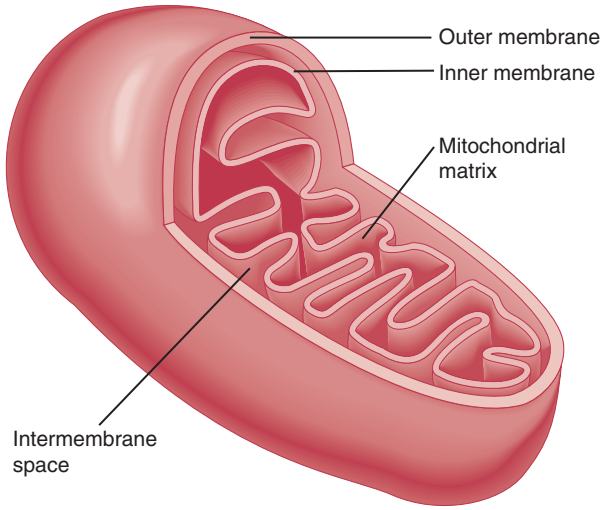


Figure 1.7 Mitochondrion. Note the inner and outer mitochondrial membranes.

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.[3,4] 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.[5] 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 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 nuclear control of mitochondrial gene expression is dependent on 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-g 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.[6,7] 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. Refer to **Special Feature 1.1** for additional information on the mitochondria in relation to disease.

SPECIAL FEATURE 1.1 Mitochondrial Diseases

Genetic, metabolic, and dietary events can result in mitochondrial diseases. Many mitochondrial diseases are due to inborn errors of metabolism that result in dysfunction of the electron transport system.[8] 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.[9] 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.[8,10] The DNA responsible for encoding cytochrome c oxidase subunit IV is present, but not the DNA of mitochondria-encoded cytochrome c oxidase subunit II.[11] Another disorder, myoclonus epilepsy with ragged red fibers, 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 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. A copper chaperone protein, called SCO2, was found to be mutated in several forms of fatal infantile cardiomyopathy leading to cytochrome c oxidase deficiency.[12] 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,[13] 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.[14] 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 one or more nuclei. As a rule, cells beget cells; therefore, all nucleated cells will contain the same DNA. Each DNA molecule contains myriad 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**).

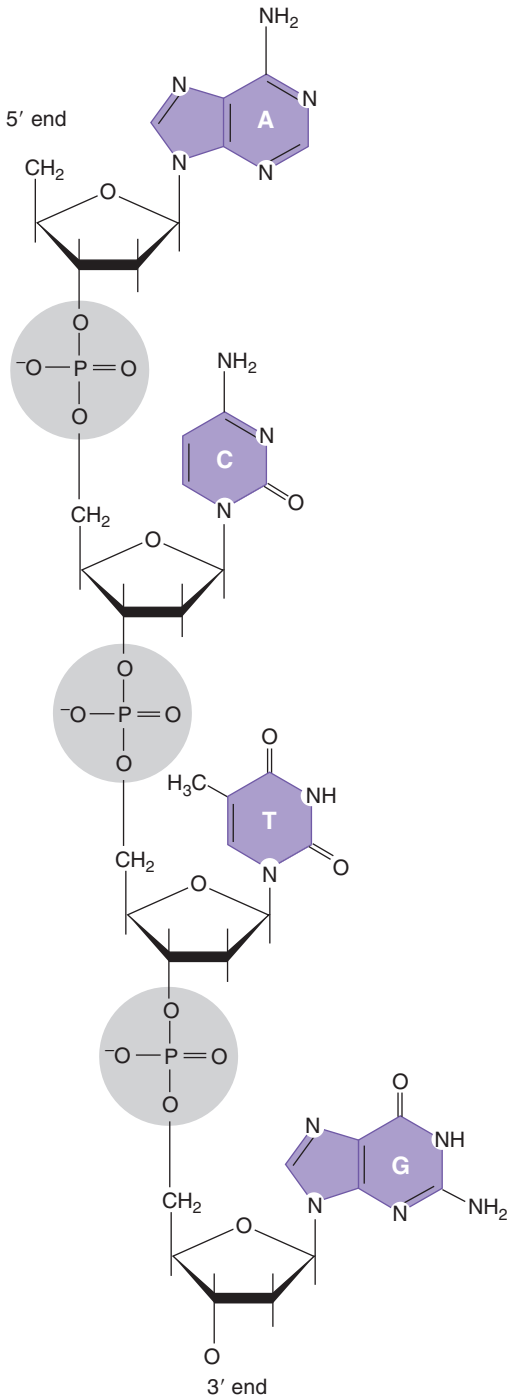


Figure 1.8 Single Strand of DNA. DNA bases linked by phosphodiester bonds, indicated by shaded areas.

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

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 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 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**).

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

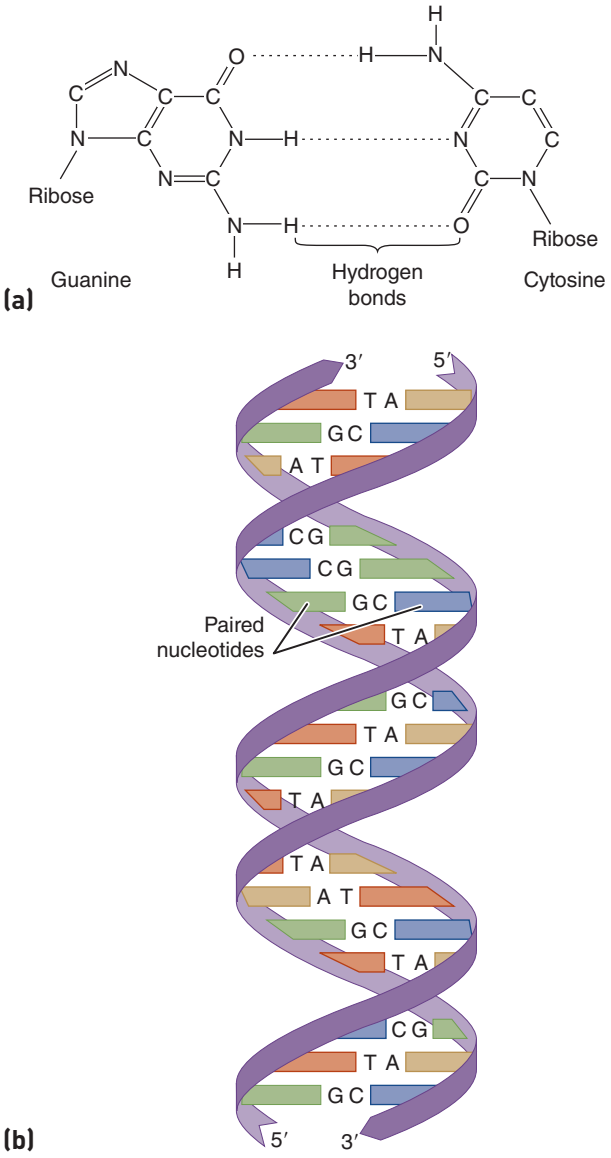


Figure 1.9 Hydrogen Bonding Between Complementary Nucleotide Bases. The hydrogen-bond link between adenine and thymine **(a)**, and hydrogen bonding between the double helical DNA strands **(b)**.

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

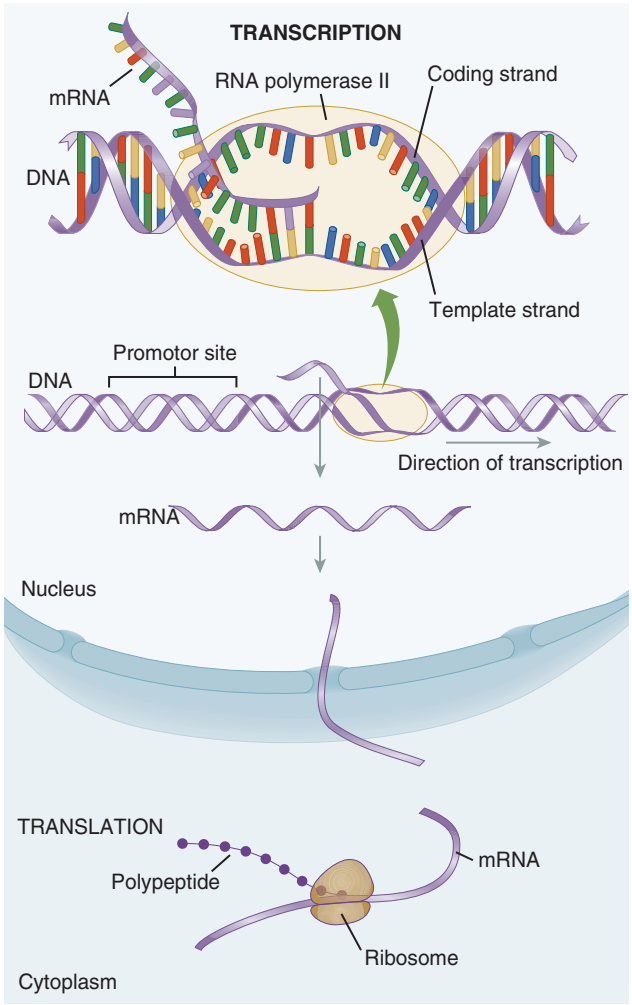


Figure 1.10 Protein Synthesis. Diagram of major steps in synthesis of protein as directed by DNA.

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.

Table 1.5 Base-Pairing of Nucleic Acid Bases

DNA–DNA	DNA–RNA
A–T	A–U
C–G	C–G

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. 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, those 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 biologic 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 biologic 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**.

Mini Case Study

Description of the Problem: Significance of Selected Nutrients in Combating Covid-19

Severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, has led to a serious pandemic that has changed the way most of us live. This is a new viral disease thought to have its origins in bats and transferred to humans. One controversy is the assertion that the virus originated from a nearby lab where highly contagious viruses are studied. Many infected with SARS-CoV-2 may not show symptoms (asymptomatic), but others may need to be hospitalized. The disease, termed Covid-19, has about a 4% mortality rate, much higher than the common flu (less than 1%). Initially, the use of public health measures such as masking, maintaining 6 feet of distance, and not gathering in enclosed areas were the tools to combat Covid-19. Simultaneously, scientists worldwide banded together and were successful in producing effective vaccines effective against Covid-19.

Bonnie Clark is a student in her mid-20s earning a PhD in human nutrition. Like most students at universities, she is well aware of the inconvenience this pandemic has brought upon us as she has had to adapt to a new way of functioning with distance learning being the primary vehicle for didactic course work and conferences among her committee members, as much of her on-campus classes did not meet. Bonnie is looking for an area to conduct her research, but she is a lab-based student, and not being able to go into the lab has provided limitations on how she can pursue her research. As a consequence of the pandemic, she starts to turn her attention more toward the science of the coronavirus that leads to Covid-19, which primarily affects the respiratory system and often results in pneumonia. Bonnie recognizes that there are certain risk factors for death from the virus, such as being elderly, obese, and/or diabetic, or having other conditions such as heart disease. However, she is concerned that there seems to be little attention to possible nutrition factors. She does know from her classes that certain nutrients can impact the immune response, and in some cases, nutrient deficiencies can make one more vulnerable to disease. Bonnie is a student at a major large university with a medical center and knows that they treat Covid-19 patients. She is starting to think more about investigating this idea, as it could lead to a dissertation topic if there is sufficient information available to make such a pursuit practical. She develops a dialogue with some nutrition faculty members and physicians who treat Covid-19 patients at her university, as well as with her classmates.

Questions:

1. What types of questions should Bonnie ask herself when starting to pursue a research topic in this area?
2. Where should Bonnie begin to determine if research has already been conducted?
3. What nutrients do you believe are "researchable" as contributing to outcomes of Covid-19 based on the current literature?

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. Those coding triplets, or codons, are the complementary base triplets originally transcribed in DNA (**Table 1.6**). 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 endoplasmic reticulum matrix. As mentioned previously, those 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

Table 1.6 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.
Ala-Alanine; Arg-Arginine; Asn-Asparagine; Asp-Aspartic Acid; Cys-Cysteine; Gln-Glutamine; Glu-Glutamic Acid; Gly-LGlycine; His-Histidine; Ill=Isoleucine; Leu-Leucine; Lys-Lysine; Met-Methionine; Phe-Phenylalanine; Pro-Proline; Ser-Serine; Term-Stop Codo; Thr-Threonine; Trp-Tryptophan; Tyr-tyrosine; Val-Valine.

acids must be activated before they can attach to their corresponding tRNA. Thus, if a synthesized protein contains 500 amino acids, 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.

Nutrition and Epigenetics

Genetic inheritance of traits has long been accepted by the sequence of base pairs comprising the DNA and their subsequent expression. We now know that factors other than base-pair sequence may affect disease and gene expression. A field of study, epigenetics, adds new information on how factors outside of base-pair sequences can lead to alteration of gene expression. Epigenetics is an evolving field of study whereby factors outside of DNA base-pair sequences can lead to heritable characteristics. Notable epigenetic factors that alter gene expression involve methylation and/or histone modification of DNA.[15,16]

There are a number of nutrients than may affect methylation of DNA because they may act as methyl donors. Such nutrients include folic acid, vitamin B_{12}, S-adenosylmethionine, choline, and betaine. Over- or undermethylation may affect gene expression patterns and alter development. Histone acylation is another mechanism by which gene expression may be altered. Methylation of histones may also impact gene expression. Nutrients such as biotin, niacin, and pantothenic acid may impact histone methylation. A good example of how such nutrients may impact disease states via epigenetics is with low folic acid intake during pregnancy, which may lead to neural tube defects. Inadequate methylation of DNA due to low dietary intake of folic acid has thought to result in the reprogramming of critical steps in the development of neural tube defects. Clearly, the interaction of key nutrients as it relates to methylation and histone acylation opens new doors to understanding the role of nutrients in disease process.

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.[17,18] 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

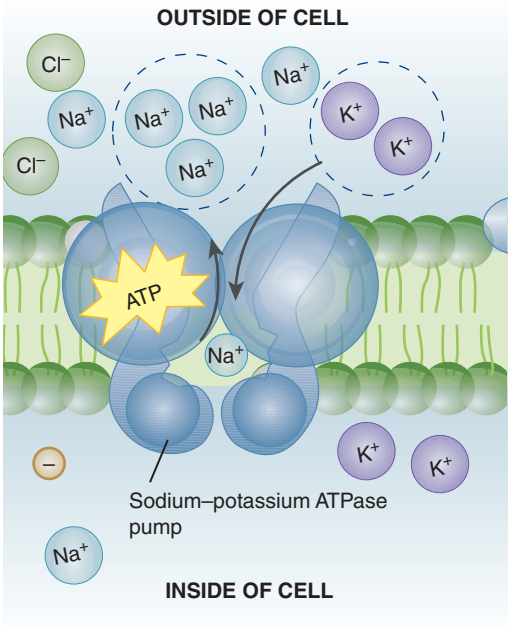


Figure 1.11 Sodium–Potassium ATPase Pump. Adenosine triphosphate (ATP) is hydrolyzed to provide the energy necessary to concomitantly pump sodium and potassium across the plasma membrane against their concentration gradient. For instance, sodium is pumped to the outside of the cell and potassium is pumped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

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.

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. Those bonds thus became known as **high-energy bonds**. When ATP is hydrolyzed to produce ADP, the change in standard Gibbs free energy ($\Delta G^{o\prime}$) 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. ADP can be broken down to adenosine monophosphate (AMP) and pyrophosphate, 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:

$$ATP + AMP \leftrightarrow 2\ ADP$$

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). Acetyl CoA enters the Krebs cycle. Oxygen is required as it is an **aerobic** process. Likewise, the breakdown of fatty acids, some amino acids, and ethanol also result in the production of acetyl CoA.

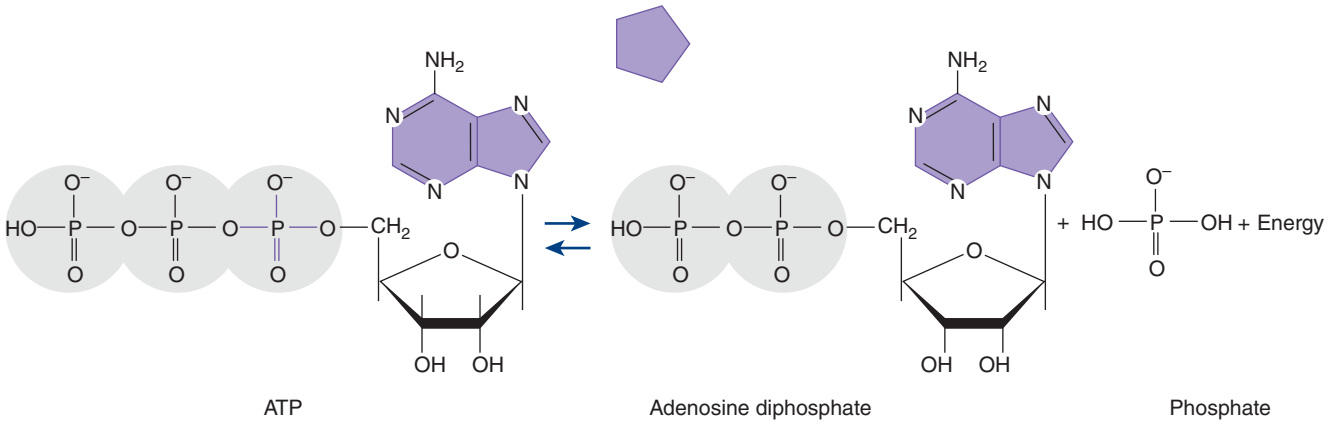


Figure 1.12 Adenosine Triphosphate (ATP). ATP is the primary high-energy molecule produced in human cells. Bonds between the phosphate groups are hydrolyzed to liberate energy, which is applied to cellular processes.

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 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**

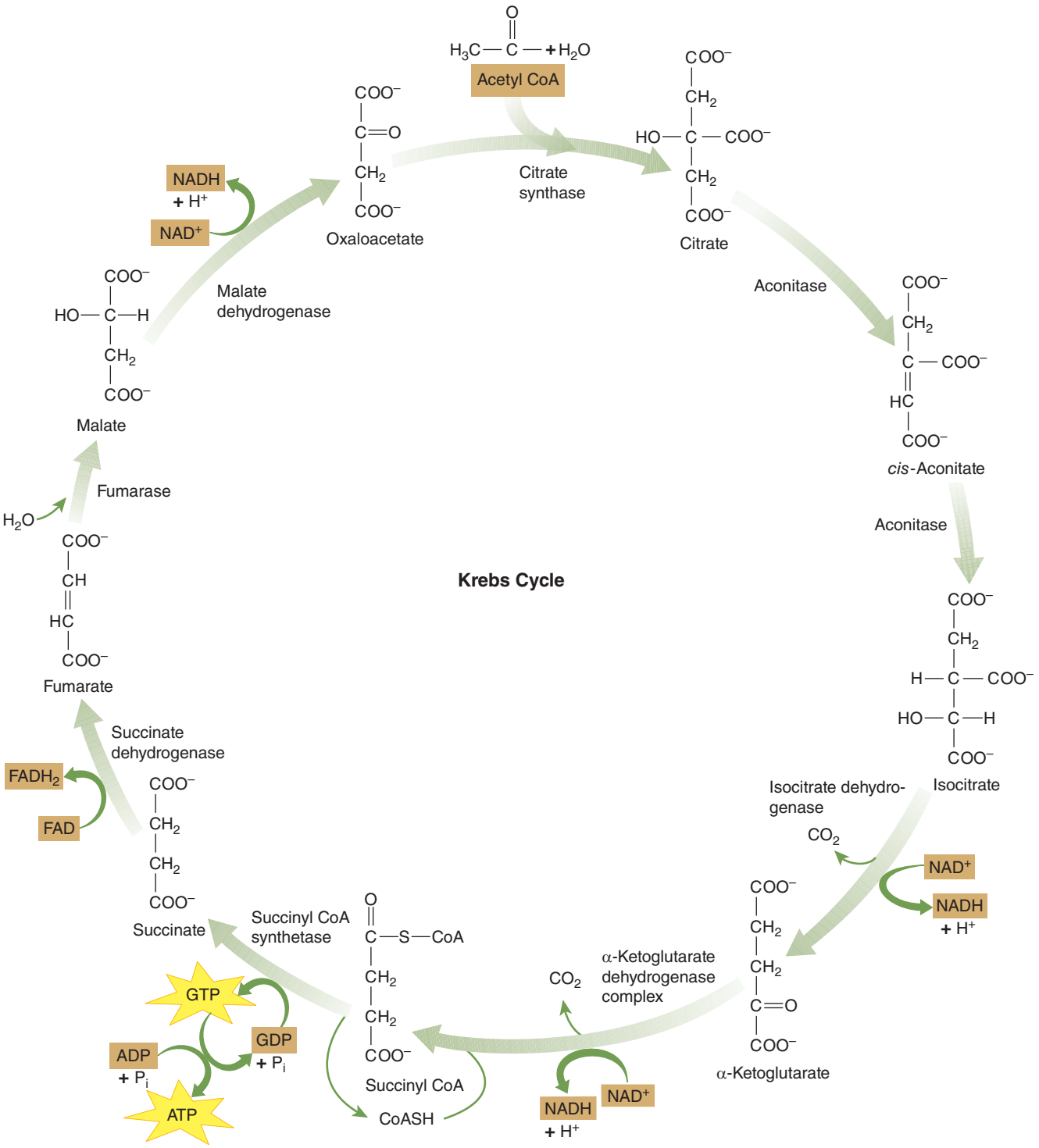


Figure 1.13 The Krebs (Citric Acid) Cycle. Basic biochemical reactions to produce NADH + H^+ and $FADH_2$ for subsequent ATP synthesis. Acetyl CoA is a major metabolite produced from the oxidation of glucose and fat.

(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 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 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**).

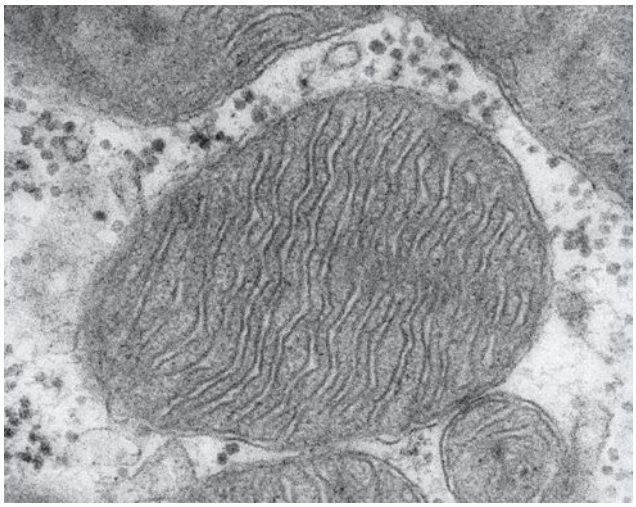


Figure 1.15 Electron Micrograph of Cardiac Myocyte Mitochondria (25,000×). Note the densely packed inner membrane, or cristae.

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 the 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.

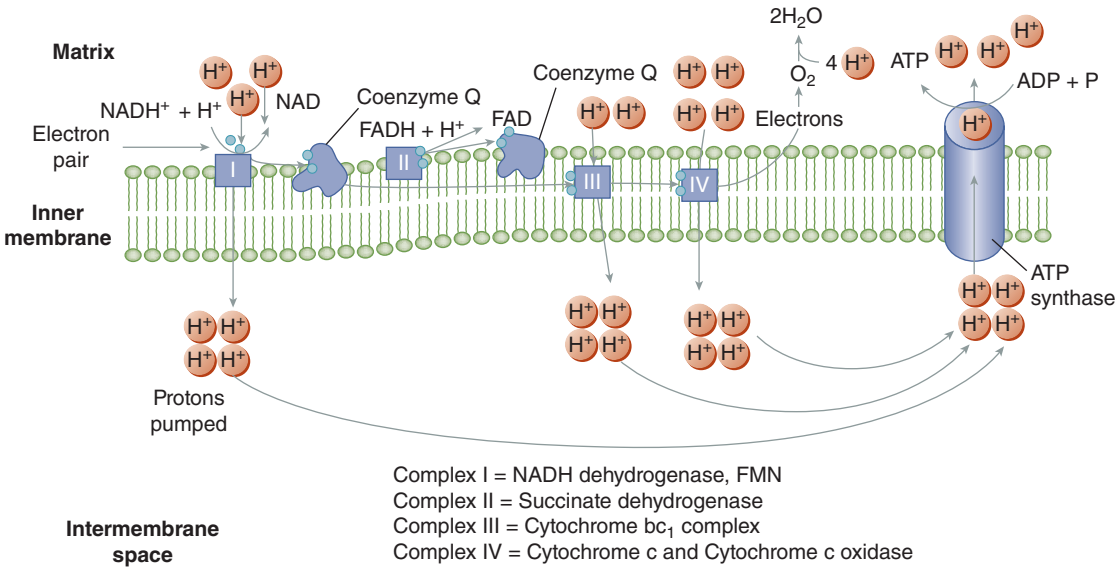


Figure 1.14 Electron Transport Chain. Note that O_2 is the final electron acceptor.

Electrons move forward through the electron transport chain toward oxygen because of the large $\Delta G^{\circ\prime}$ gradient. The transfer of electrons from NADH to oxygen 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 oxygen 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 a series of iron-sulfur (Fe-S) complexes to coenzyme Q. 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 chemoelectric 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 they 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 posttranscriptional modification?
3. Explain how the breakdown products eventually end up being metabolized in the Krebs cycle.
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 those 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

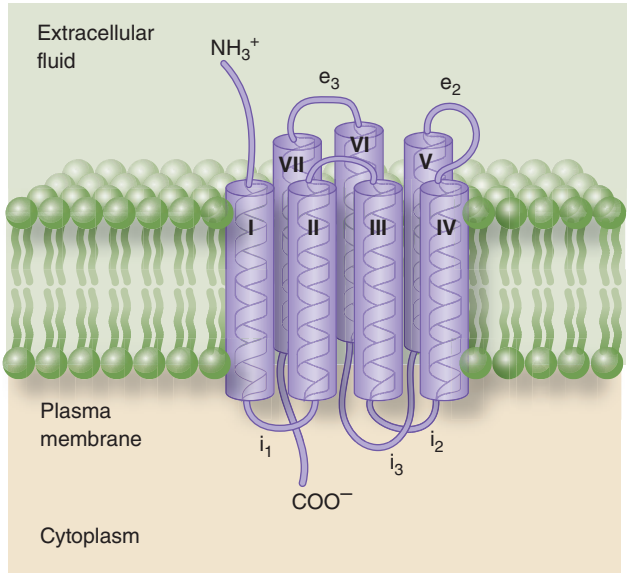


Figure 1.16 Structure of a Transmembrane Protein Receptor.

Data from Bockaert, J. *Encyclopedia of Life Sciences.* John Wiley & Sons, Ltd., January 2006. [doi:10.1038/npg.els.0000118].

cell. **Special Feature 1.2** describes what is considered the lost organelle: Peroxisomes.

Enzymes

All enzymes are composed of proteins. Some of those 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 create a reaction. The energy 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

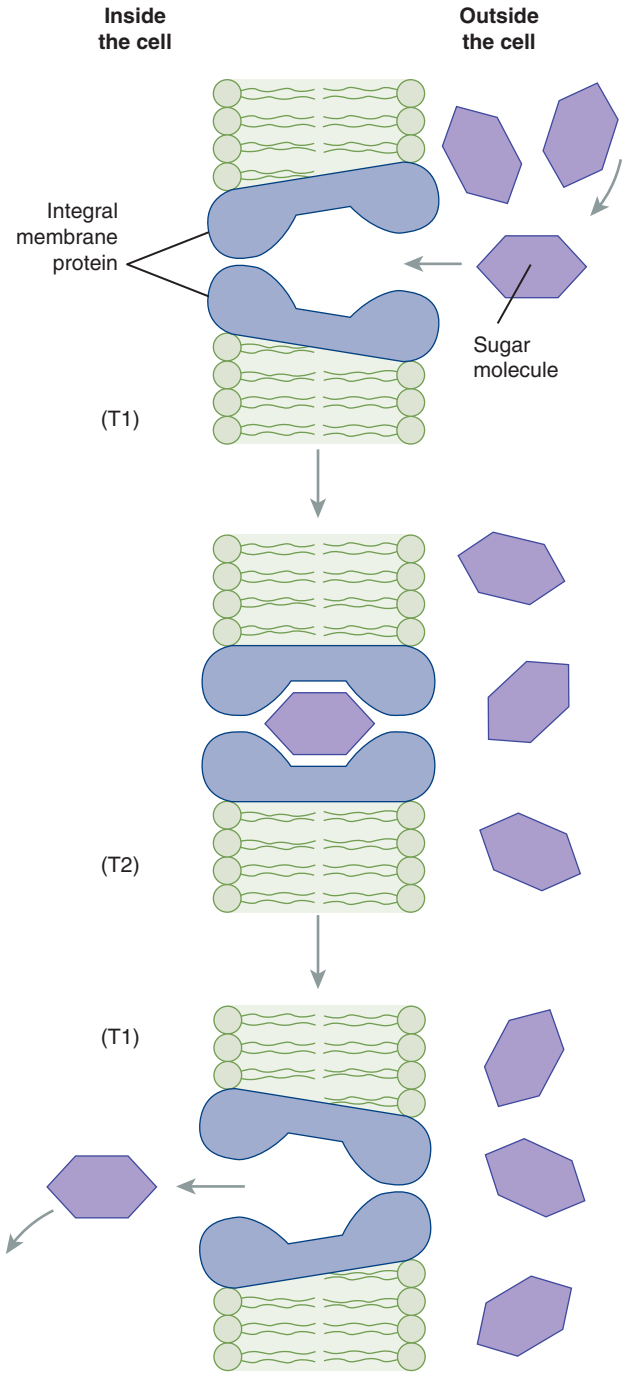


Figure 1.17 Conformation Change of Some Transmembrane Receptors When Importing or Exporting a Substance. In this case, note the change in the transport protein for a sugar molecule as it goes from the outside to the inside of the cell. T1 is the transport protein without a sugar molecule, and T2 is the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

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.

SPECIAL FEATURE 1.2 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.[19] 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). PPARα is just one type of PPAR. PPARα is very important in controlling lipid anabolism or catabolism by influencing enzymes involved in lipid metabolism. 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. Lipid metabolism is discussed in more detail in Chapter 5.

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

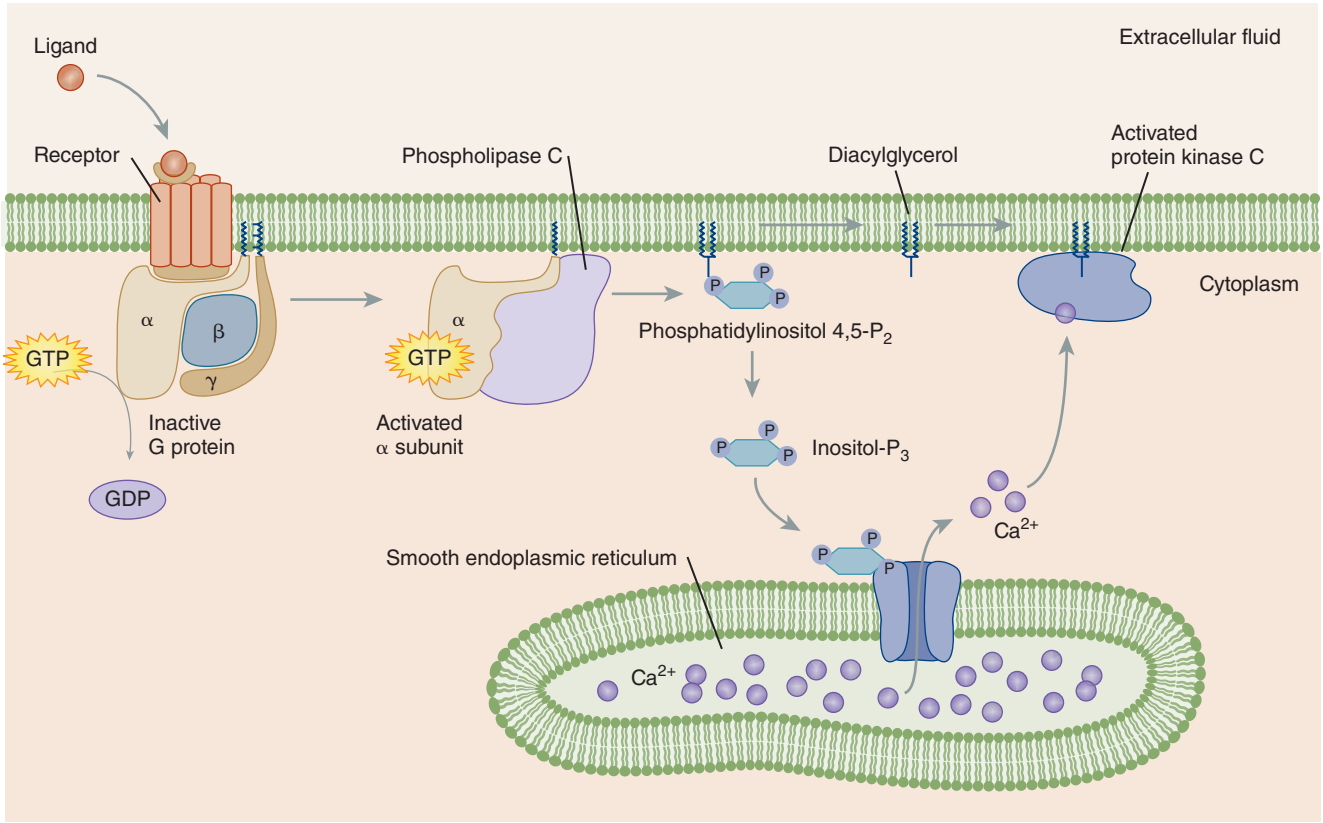


Figure 1.18 Cell Signaling Example. A hormone (ligand) interacting with a receptor and a G protein to generate a second messenger, in this case, inositol-P_3.

Data from an illustration by George M. Helmkamp, Jr., School of Medicine, University of Kansas.

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—rather, it 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 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 diffusion (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 cotransport mechanism requiring ATP. (**Cotransport** 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 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 (adrenalin) and the thyroid hormones (triiodothyronine and thyroxine). Steroid hormones are made from cholesterol and include testosterone, estrogens, cortisol, progesterone, and aldosterone.

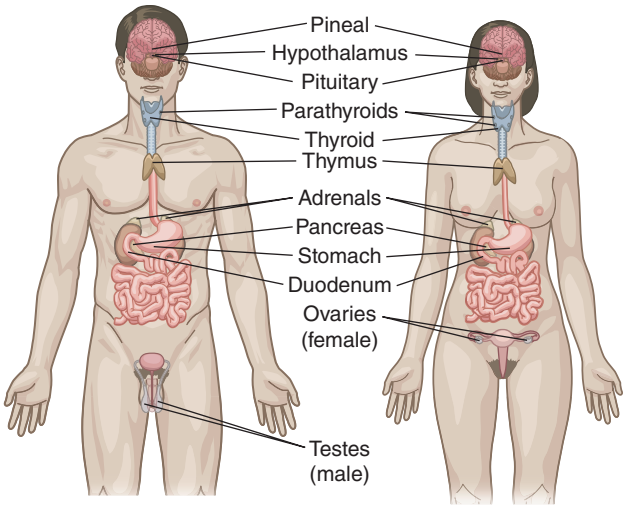


Figure 1.19 Endocrine Organs. Major synthesis sites for different hormones.

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 calcium, cyclic guanosine monophosphate (cGMP), inositol triphosphate, and diacylglycerol. Other hormones, such as thyroid hormones and steroid-based hormones, have nuclear receptors. Those hormones exert their activity by influencing gene expression (**Table 1.7**).

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 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 those complexes is to turn a gene on, or initiate the transcription process.

Table 1.7 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 water loss by kidneys by increasing water 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

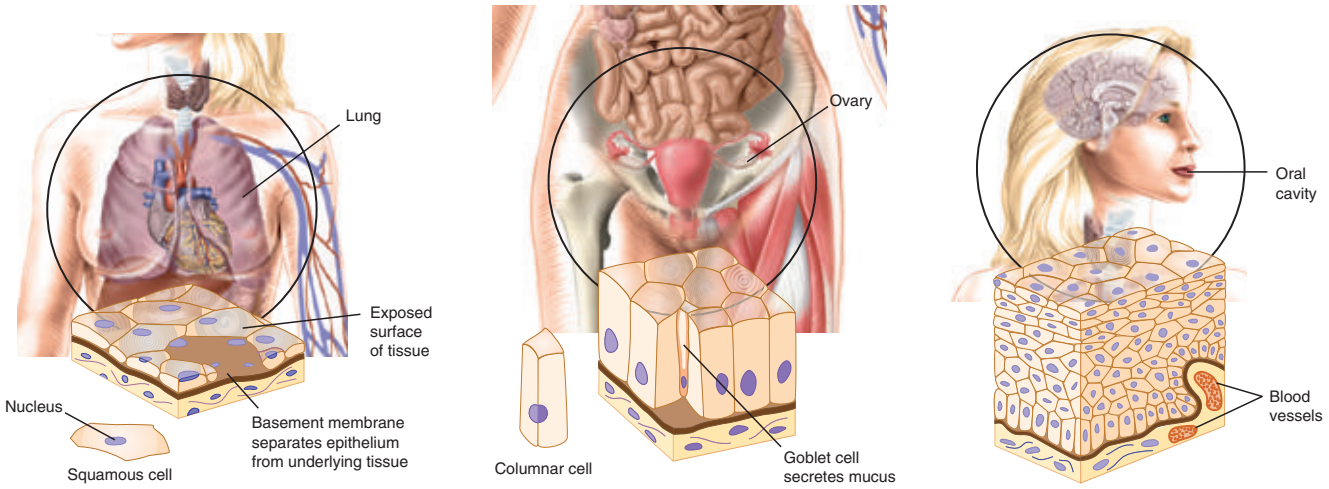
BEFORE YOU GO ON . . .

1. What does an enzyme 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 compared with active transport?

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 those 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



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

(a)

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

(b)

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

(c)

Figure 1.20 Epithelia. Different types of epithelia include simple squamous **(a)**, columnar **(b)**, and stratified squamous **(c)**. Cuboidal cells not shown.

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

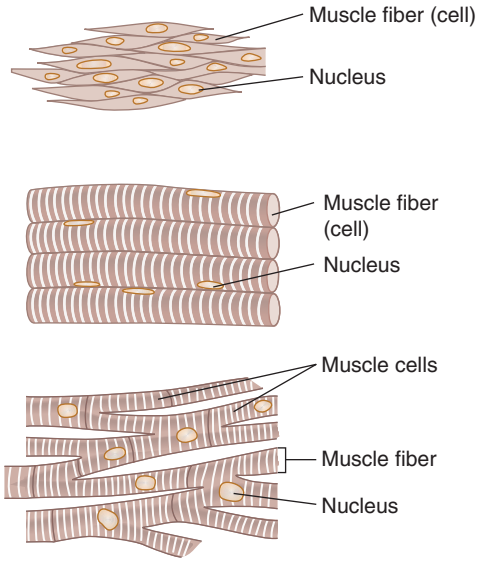


Figure 1.21 Muscle Cell Types. Muscle cell types in the human body: smooth, skeletal, and cardiac.

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 1.8** lists the 10 organ systems in the human body and their component organs.[20]

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.

Table 1.8 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, 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

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 physical stresses, such as those produced during 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

Nerve cells

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,

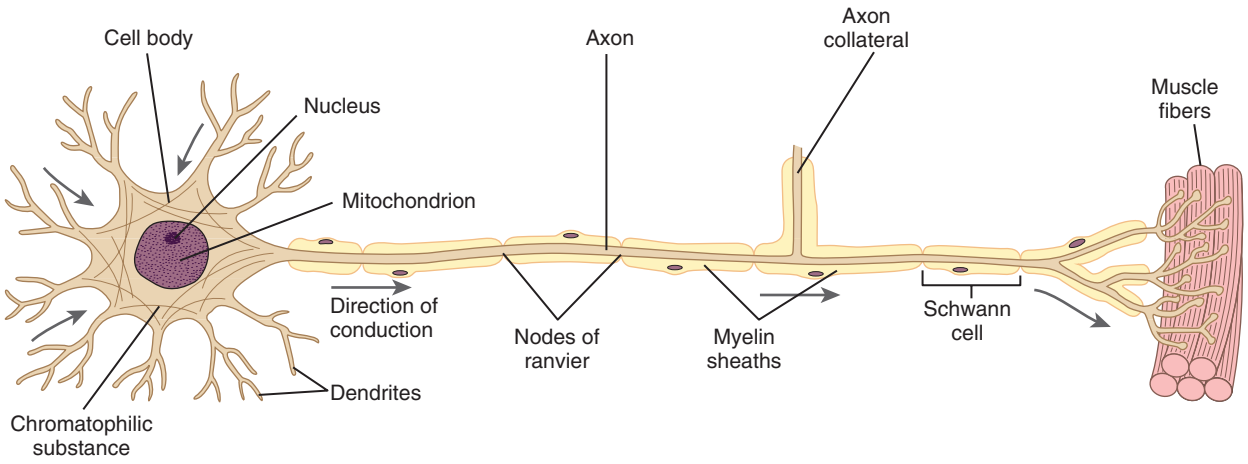


Figure 1.22 General Neuron Structure. Structure of nerve cell and overview of signal transmission from the cell body via the axon to the target structure.

ears, eyes) and inside the body. Those 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 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 those are opened (**Figure 1.23**).

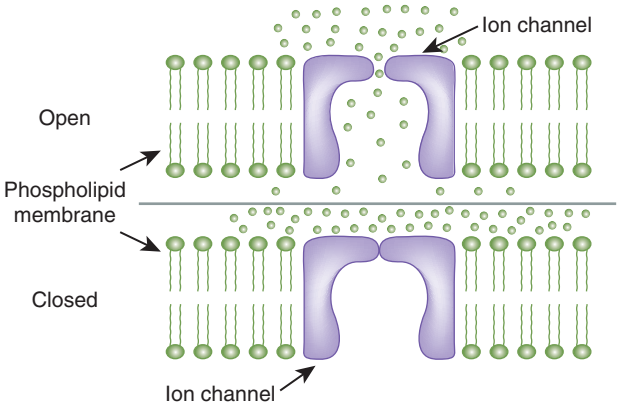


Figure 1.23 Ion Channel. The regulated opening of ion channels allows for rapid diffusion across the membrane.

Neurotransmission

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 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.

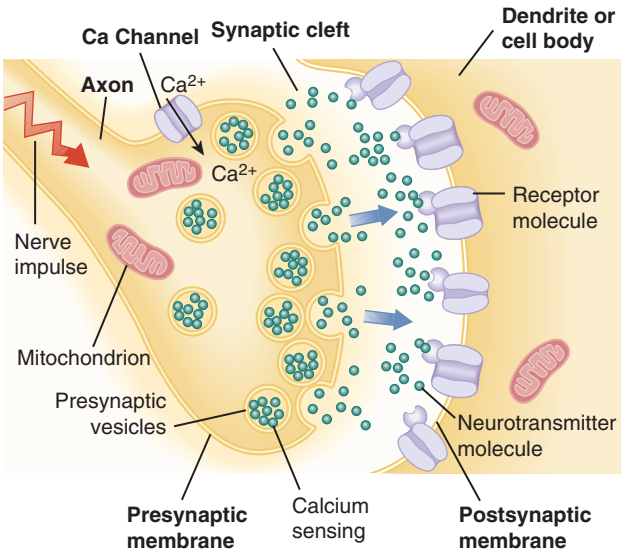


Figure 1.24 Axon Terminal Synapsing with Target Cell. The axon is shown. Neurotransmitter release and action on adjacent cells occur via receptor molecules on the postsynaptic membrane. Here the neurotransmitter is acetylcholine, which will react with a receptor molecule on skeletal muscle cells and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

The Brain

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

The spinal cord is approximately 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, at 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 fiber-like units called **myofibrils**. Myofibrils can account for as much as 80% of a muscle cell's volume. Each myofibril is a stalk-like collection of protein (**Figure 1.25**). The predominant proteins are **actin** and **myosin**, which are referred to as thin and thick filaments, respectively. They are organized into a tiny contraction region called a **sarcomere**, which sits next to adjacent and connected sarcomeres (**Figure 1.26**). Other proteins associated with the sarcomeres are **troponin** and **tropomyosin**. Those proteins are involved in regulating the contraction of sarcomeres.

When skeletal muscle cells are stimulated, calcium 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

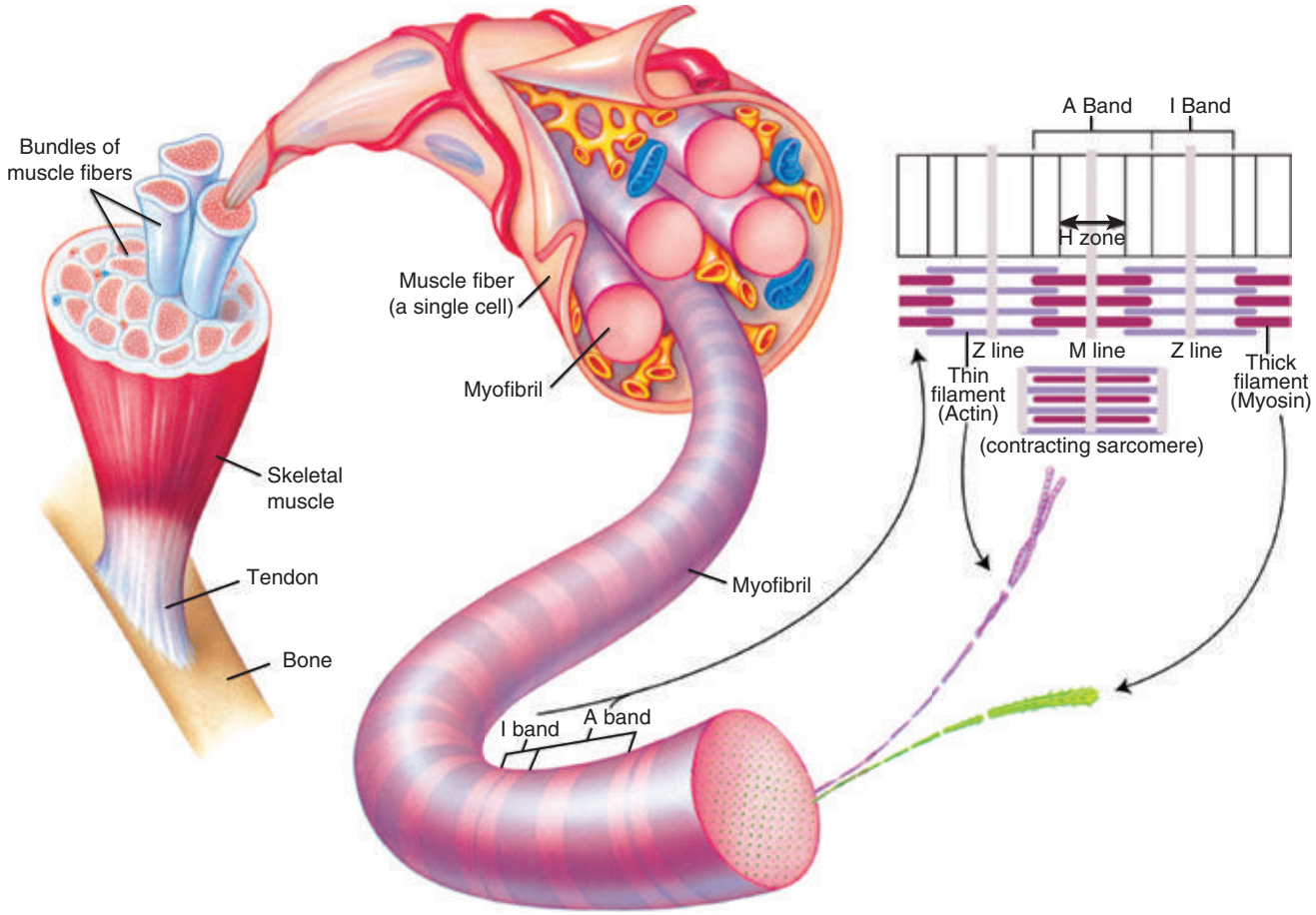


Figure 1.25 Skeletal Muscle Components. Diagram represents the ultrastructure aspects of the muscle (actin and myosin) and how they relate to a myofibril. The diagram then demonstrates how the myofibril composes muscle fiber bundles, and how the bundles compose the skeletal muscle.

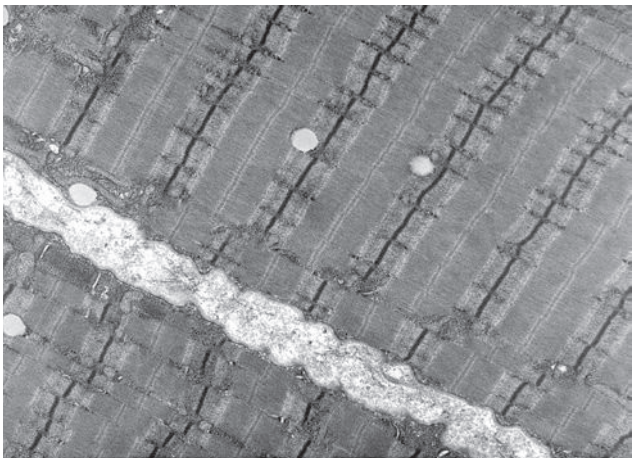


Figure 1.26 Electron Micrograph of Adjacent Sarcomeres (27,000×). Note the banding arrangement.

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

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 Heart

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.

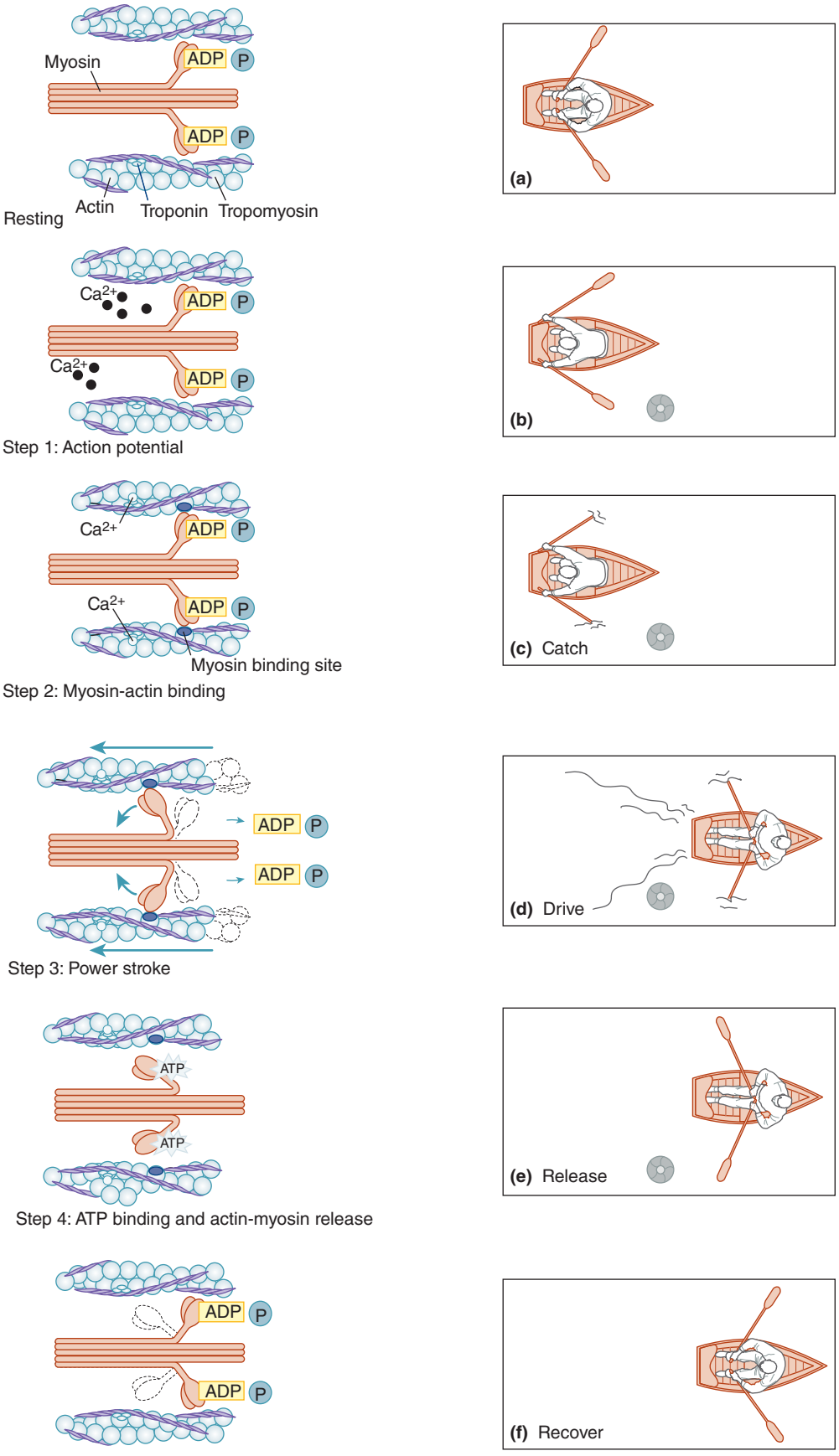


Figure 1.27 Calcium Binding to Troponin. Calcium binding to troponin results in the movement of tropomyosin and the revealing of myosin binding sites on actin. This allows myosin to bind and myofibrils to contract.

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 carbon dioxide 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 the cardiac muscle are the same as the 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 2 billion times throughout a human being's life.

Blood

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 approximately 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.

The remaining components of blood are the **leukocytes** (white blood cells) and **platelets**, which collectively make up approximately 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 oxygen molecules, each red blood cell has the potential to transport 1 billion molecules of oxygen.

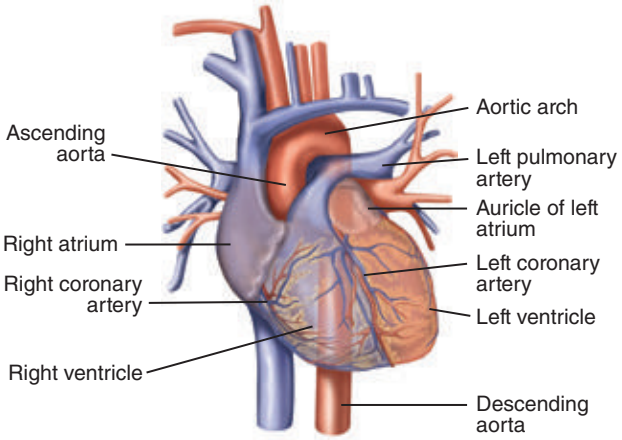


Figure 1.28 Human Heart. The major blood vessels are also shown.

Circulation

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, carbon dioxide exits the blood and enters into the lungs. It is then removed during exhalation. At the same time, oxygen 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 into 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, into 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 oxygen and release carbon dioxide. 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)